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Computational Study on SARS-CoV-2 Viral Protein Interaction with Natural Compounds of *Coriandrum sativum* L

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Abstract— **The SARS-COV-2 become a global pandemic causing significant mortality and morbidity all around the world. Until now there are no effective drugs or vaccines available against SARS-CoV-2. In this regard, medicinal plants captured enormous attention, as natural products are safe and easily available bioactive compounds in which maintain the disease homeostasis. Amongst, natural compounds of *Coriandrum sativum* L (coriander) have proved to be effective in viral infection, as they possess antiviral and anti-inflammatory activities. However, molecular regulation of such bioactivities remains elusive. We performed molecular docking analyses using AutoDock Vina to investigate the potential inhibitory activities of the seven natural compounds of coriander (limonene, geraniol, gamma-terpinene, geranyl acetate, caffeic acid, ferulic acid, gallic acid) against the essential proteins of SARS-CoV-2 (main protease (Mpro), nonstructural protein-13 (NSP-13), Papaine like protease (PLpro) and RNA dependent RNA polymerase(RdRp)) together with two main inflammatory proteins (cyclooxygenase-2 (COX-2) and interleukin-6 (IL- 6)). The empirical and knowledge-based algorithm of AutoDock Vina was utilized to calculate free binding energies of ligands and BIOVIA discovery studio 2020 tool was used to visualize docking results. Our results reveal that gallic acid has a strong binding affinity to Mpro (-5.8 kcal/mol) and NSP13 (-7.0 kcal/mol) forming five and three conventional hydrogen bonds respectively. Further, caffeic acid demonstrates a higher binding affinity to PLpro (-7.4 kcal/mol) and RdRp (-6.7 kcal/mol) while securing four and three conventional hydrogen bonds respectively. Interestingly, both COX-2 (-6.9 kcal/mol) and IL-6 (-6.3 kcal/mol) also show a higher binding affinity to gallic acids. In addition, gallic acid stabilizes three conventional hydrogen bonds with COX-2 whereas it forms four conventional hydrogen bonds with IL-6. Further, drug-likeness properties of gallic acid and caffeic acid were determined using the SWISSADME server. Our results show that both gallic acid and caffeic do not violate Lipinski rules suggesting these compounds as new antiviral and anti-inflammatory drug candidates for SARS-CoV-2.**

Keywords-Viral Protein, Docking, CoV-2

I. INTRODUCTION

Since at the end of the 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) disease become a worldwide pandemic showing significant mortality and morbidity every corner of the world [1]. The control of SARS-CoV-2 is a great challenge as the virus has diverse transmission modes and the presence of asymptomatic careers in the human population [2]. However, to date, there are no promising drugs or vaccines available to control SARS-CoV-2 infection. As a result, *in silico* drug repurposing using natural compounds of medicinal plants captured great attention to developing fast and efficient drugs against SARS-CoV-2.

Ayurveda, a traditional system of medicine has been acknowledged as an essential aspect of treatment for infectious diseases over 3000 years ago [3]. Since then, a plethora of medicinal and aromatic plants gained enormous attention as herbal therapeutics as they have natural compounds in which maintain the disease homeostasis [4]. Amongst, *Coriandrum sativum* L (coriander) is a well-known medicinal plant in traditional medicine [5], [6].

The health properties of coriander have been linked to alleviating numerous ailments including bacterial infections, viral infections [5]–[7]. There, it has been illustrated that coriander seed extract has potent antibacterial activity against *Klebsiella pneumonia*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* [8]–[10]. Moreover, the essential oil of coriander seed, linalool has been illustrated anti-cancer activity as it tends to downregulate cell proliferation in cancer tissues [11]–[13]. In addition to antibacterial activity, several studies have been investigated the anti-inflammatory activity of coriander extracts [14], [15]. To that end, a recent study revealed that traditional coriander concoction possesses potent anti-inflammatory activity together with immunomodulatory activities [6]. Besides, coriander seed extract has also been utilized as potential antiviral therapeutics. For example, dichloromethane demonstrated antiviral activity against the human immunodeficiency virus (HIV) [16]. It has also been shown that coriander seed extracts inhibit hepatitis A (HAV) viral replication *in vitro* [16]. Further, computational studies have been revealed that some natural compounds of coriander extract exhibit strong binding affinity towards structural and non-structural proteins of the Dengue and MERS corona viruses [16]. There, E-2-dodecanol exerts the highest binding affinity with most of the structural proteins of the Dengue virus whereas it binds to most of the structural proteins of the MERS virus. On the contrary, dodecanal has been demonstrated a strong binding affinity towards the nonstructural proteins of Dengue virus and MERS virus [16]. Concerning this, the prophylactic and therapeutic potential of traditional medicine systems attains great attention with the current Corona pandemic. There, boiled coriander seed extraction was recommended as adjuvant therapy of SARS-CoV-2 infection [3], [4], [17].

Essentially, the SARS-CoV-2 viral genome encodes essential non-structural (NSP) and structural proteins. There, the open reading frames: ORF1a and ORF1b at the 5' region of the viral genome encode two polypeptides namely, pp1a and

pp1ab [18]. These two polypeptides collectively form 16 NSPs. Amongst NSPs, Chymotrypsin-like protease (3CLpro) or main protease (Mpro), papain-like a protease (Ppro) RNA dependent RNA polymerase (RdRp) and NSP13 (helicase) have been identified as the key proteins in which regulate the virus life cycle. The remaining region of the viral genome encodes the four main structural proteins: Spike protein (S), Envelope protein (E), Membrane protein (M) and Nucleo capsid protein (N) [1], [19].

In general, cyclooxygenases (COX-1 and COX-2) are among the major inflammatory proteins upon viral infections in humans [20]. COX-1 is usually involved in the formation of the blood clot and maintain gastric acidity while COX-2 is typically induced pain during inflammation in specific tissues [20], [21]. In addition, increase levels of circulating cytokines such as interleukins (IL) have been identified as one of the major reasons for multiorgan failure associated with SARS-CoV-2 patients [22]. Among the ILs, IL-6 illustrates predominant proinflammatory activities in the respiratory system associated with acute respiratory distress syndrome and respiratory failure in SARSS-CoV-2 patients [23]. Therefore, inhibition of the activities of viral proteins and host inflammatory proteins using natural compounds would provide a promising approach to the control SARS-CoV-2 virus life cycle and to reduce the severe inflammatory conditions associated with SARS-CoV-2 infection. To this end, we selected limonene, geraniol, gamma-terpinene, geranyl acetate, caffeic acid, ferulic acid, gallic acid of coriander as potential natural inhibitors. Further, we selected Mpro, PLpro, RdRp and NSP13 as SARS-CoV-2 viral target proteins together with human inflammatory proteins, COX-2 and IL-6. In the molecular docking study using AutoDock vina, we show that gallic acid is a potential inhibitor of Mpro and NSP13 while caffeic acid is a potential inhibitor of PLpro and RdRp. Interestingly, we demonstrate that caffeic acid has a strong binding affinity with both COX-2 and IL-6. Furthermore, the pharmacokinetic analysis predicts that both gallic acid and caffeic acid as novel oral drugs to cure SARS-CoV-2.

II. Objectives

The objective of the study is to decipher the antiviral and anti-inflammatory activities of natural compounds of coriander against SARS-CoV-2 viral infection using *in silico* molecular docking analysis. The findings obtained from the *in silico* docking approaches could easily be tested in *in vitro* or *in vivo* conditions to determine safe antiviral and/or anti-inflammatory treatment.

III. Methodology

A. *Obtaining ligand compunds*

The natural compounds (ligands) molecules namely limonene, geraniol, gamma-terpinene, geranyl acetate, caffeic acid, ferulic acid, gallic acid were identified as potential ligand hits from the literature [24]. The two-dimensional (2D) structure of the ligands was obtained from PubChem database (https://pubchem.ncbi.nlm.nih.gov/) and the spatial coordinates of the ligands were obtained as a spatial data file in .SDF format.

B. *Obtaining Protein Structure*

The crystal structure of 3-chymotrypsin-like protease (3CLpro/Mpro, PDB ID: 6Y2F),[25] papain-like protease (PLpro, PDB ID: 7CMD),[26] nonstructural protein (NSP13: helicase, PDB ID; 6ZSL) [27] and cyclooxygenase 1 (COX-2, PDB ID: 5KIR) [21] and Interleukin 6 (IL-6, PDB ID: 1ALU) [28] were retrieved from the Research Collaboratory for Structural Bioinformatics Protein Databank (RCSB PDB), https://www.rcsb. org [29] in .PDB format.

C. *Ligand Preparation for Molecular Docking*

Energy minimization of the ligand molecules is essential to determining their proper molecular coordinates [30]. Thus, the energy minimization is performed until a ligand molecule reaches its local minimum energy value to form the most stable conformation of the ligand. Open babel tool was implemented to perform, energy minimization of all the ligands in .SDF using MMFF94 force field together 1000 geometry optimization steps [31]. Further, Gaste.ger-Marsili sigma partial charges (gasteiger) were assigned to ligand molecules and saved in .PDBQT format.

D. *Protein Preparation*

Auto dock tool was used to prepare the target protein molecules [32]. Initially, all the co-crystalized water molecules were removed, and polar hydrogen atoms were added. Next, Kollman united atom type charges were added and saved the protein molecule in PDBQT format.

E. *Molecular Docking*

We performed molecular docking analyses to investigate the potential inhibitory activities of the ligands towards the essential proteins of SARS-CoV-2 and host inflammatory proteins as potential inhibitors. We performed blind docking considering the entire surface of proteins as binding sites other than their active site. Thus, all the grid parameters and conFig.uration files were generated based on the blind docking. In addition, all the protein molecules were maintained as rigid receptors (rigid docking) while optimizing the structural conformations of the ligands during the docking process. Finally, the docking procedure was carried out by using AutoDock Vina which implies a gradient optimization algorithm [33] using default parameters. A shell script provided in AutoDock Vina was run on a Linux terminal during docking simulation.

The free binding energy of ligands was calculated using empirical and knowledge base scoring function provided by AutoDock Vina. By default, the scoring function calculates nine free binding energies. Of nine, we selected the highest value as the best interaction binding energy (kcal/mol). The intermolecular hydrogen bonding, hydrophobic interactions, and pi-stacking interactions were analyzed to determine the effective inhibitory activity of the protein-ligand complex.

F. *Results Visualization*

The three/dimensional structure of protein-ligand complex was visualized using BIOVIA Discovery Studio 2020 (Dassault Systemes BIOVIA, 2020) and two/dimensional pose of the protein-ligand complex was visualized using PoseView of Protein plus web server (https://proteins.plus) [34].

IV. Results and Discussion

In Sri Lanka, it has been shown that concoction made by coriander is used as an adjunct therapy to control SARS-CoV-2 infection [17]. However, there was no research evidence to show the molecular regulation of coriander during SARS-CoV-2 infection. In this study, we investigate the molecular regulation of natural compounds of coriander in the context of molecular docking simulations.

A. *Calculation of binding free energy and Amino acid interaction with phyto-compounds for SARS-CoV-2 viral proteins*

We calculated the binding energies of the aforementioned ligands through AutoDock Vina. Results show that gallic acid has a strong binding affinity to Mpro (-5.8 kcal/mol, Table 1) and NSP13 (-7.0 kcal/mol, Table 1) among the other compounds. Caffeic acid demonstrates the highest binding affinity to PLpro (-7.4 kcal/mol, Table 1) and RdRp (-6.7 kcal/mol, Table 1). Moreover, our molecular docking simulations further illustrate that Trp207 (tryptophan), Lys5 (lysine), Leu282 (leucine) and Phe3 (phenylalanine) of the Mpro are firmly bound with gallic acid forming five conventional hydrogen bonds (Fig. 2A-C: black dashed lines). Similarly, gallic acid secured three conventional hydrogen bonds with Arg409 (arginine), Phe422 (phenylalanine), and

Asn381 (asparagine) at the active site of NSP13 (Fig. 2D-F: black dashed lines). The caffeic acid stabilized at the active site of the PLpro forming four conventional hydrogen bonds with Tyr273 (tyrosine), Thr301 (threonine) and Tyr264 (tyrosine) (Fig. 2G-I: black dashed lines) and a pi-stacking (parallel) interaction between the ligand, and Tyr264 (Fig. 2I: green dashed line). Additionally, we observed Lys50, Lys121 and Thr120 residues form three conventional hydrogen bonds together (Fig. 2J-L: black dashed lines) an amide-pi stacked interaction with Arg55 residue (Fig. 2L: green dashed line) in RdRp. These results demonstrate that caffeic acid and gallic acid can be used as potential drugs molecules during viral infections as they form strong conventional hydrogen bonds with amino acids of SARS-CoV-2 proteins.

B. *Calculation of binding free energy and Amino acid interaction with phyto-compounds for host inflammatory proteins.*

We hypothesize that natural compounds of coriander will also inhibit the host inflammatory proteins thereby downregulating the inflammation pathway. Thus, we selected two main inflammatory proteins, cyclooxygenase-2 (COX-2) and interleukin-6 (IL-6) to evaluate the potential inhibitory activities exert by the selected ligands. Our results reveal that gallic is having the highest binding affinity to both COX-2 (6.9 kcal/mol) and IL-6 (6.3 kcal/mol) compared to the other ligands. Moreover, gallic acid established three conventional hydrogen bonds with COX-2 with Thr206 (threonine) and His207 (histidine) (Fig. 3A-C) while it secured four hydrogen bonds with Arg104 (arginine), Phe105 (phenylalanine), Glu106 (glutamine), and Asp106 (aspartic acid) in IL-6 (Fig. 3D-F). In addition to hydrogen bonds, we observed that gallic acid forms one pi-stacking interaction and one amide-pi stacked interaction with Phe105 and Arg104 of IL-6 (Fig. 3F). The binding affinity of ligands generated using a docking algorithm is not sufficiently described those ligands can form a stable protein-ligand complex. Therefore, the molecular dynamics (MD) simulation of the protein-ligand complex can be performed along with the molecular docking studies to validate the binding stability of docked complexes.

C. *Analysis of Druglikeness prediction*

We evaluated the drug-likeness of these compounds taking Lipinski's rule of five (RO5) into account [35], [36]. According to the RO5, a molecule with a molecular mass (MW) less than 500 Da, no more than 5 hydrogen bond donors (HBD), no more than 10 hydrogen bond acceptors (HBA), and an octanol-water partition coefficient log Po/w (iLOGP) not greater than 5 has a great chance administer as an oral drug. Fascinatingly, we detected that both gallic acid and caffeic acid do not violate Lipinski's rule of five (Table 2). This indicates these molecules can be used as successful oral drug molecules against SARS-CoV-2. However, *in vivo* and *in vitro* experiments need to be carried out to confirm these bioactivities. As mentioned previously, we hypothesize that taking boiled coriander seed extraction as an adjuvant therapy could probably inhibit the activities of viral proteins, which are essential to maintain the virus life cycle in the host cell, consequently, decrease the viral load. Similarly, these natural compounds seem to inhibit the activities of inflammatory mediators such as IL-6 and COX-2 in the host cells that resulting in downregulation of inflammatory pathways. Collectively, these results suggest that natural compounds of coriander possess cooperate inhibitory activities targeting a diverse range of proteins thereby reduce the viral infection and host inflammatory reactions. Several studies have also been shown that some natural compounds exert their biological activities targeting a range of proteins [37], [38]. For example, it has been recognized that flavonoids such as apigenin, vitexin, quercetin, rutin, and naringenin exert antiviral activities by inhibiting viral proteases, polymerases, *etc* [39]. Therefore, the capability of natural compounds to interact with different proteins demonstrate their functional diversity suggesting them as potential drug molecules. Our results interpret those natural compounds of coriander possess strong antiviral and anti-inflammatory activities targeting a range of proteins. However, the exact bioactivities of these natural compounds should further need be tested using appropriate *in vivo* and *in vitro* biochemical assays and using other biophysical & structural experiments.

Table 1 ILLUSTRATION OF BINDING FREE ENERGY OF PHYTO-COMPOUNDS WITH SARS-COV-2 VIRAL PROTEINS

Protein Name	Compound	Binding free Energy (kcal/mol)
Mpro	Gallic acid	-5.8
	gamma-terpinene	-5.7
	limonene	-5.6
NSP13	Gallic acid	-7.0
	Ferulic acid	-6.6
	Caffeic acid	-6.5
PLpro	Caffeic acid	-7.4
	Geranyl acetate	-7.1
	Geraniol	-6.5
RdRp	Caffeic acid	-6.7
	Gallic acid	-6.3
	limonene	-6.3
COX	Gallic acid	-6.9
	caffeic acid	-6.6
	gamma-terpinene	-6.3
IL/6	Gallic acid	-6.0
	Ferulic acid	-5.3
	Geraniol	-5.3

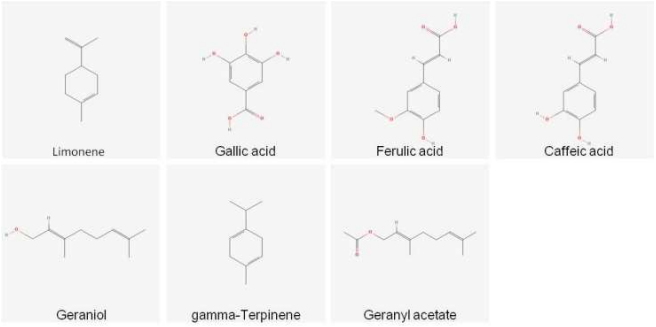

Fig. 1: Illustration of phyto-compounds of coriander

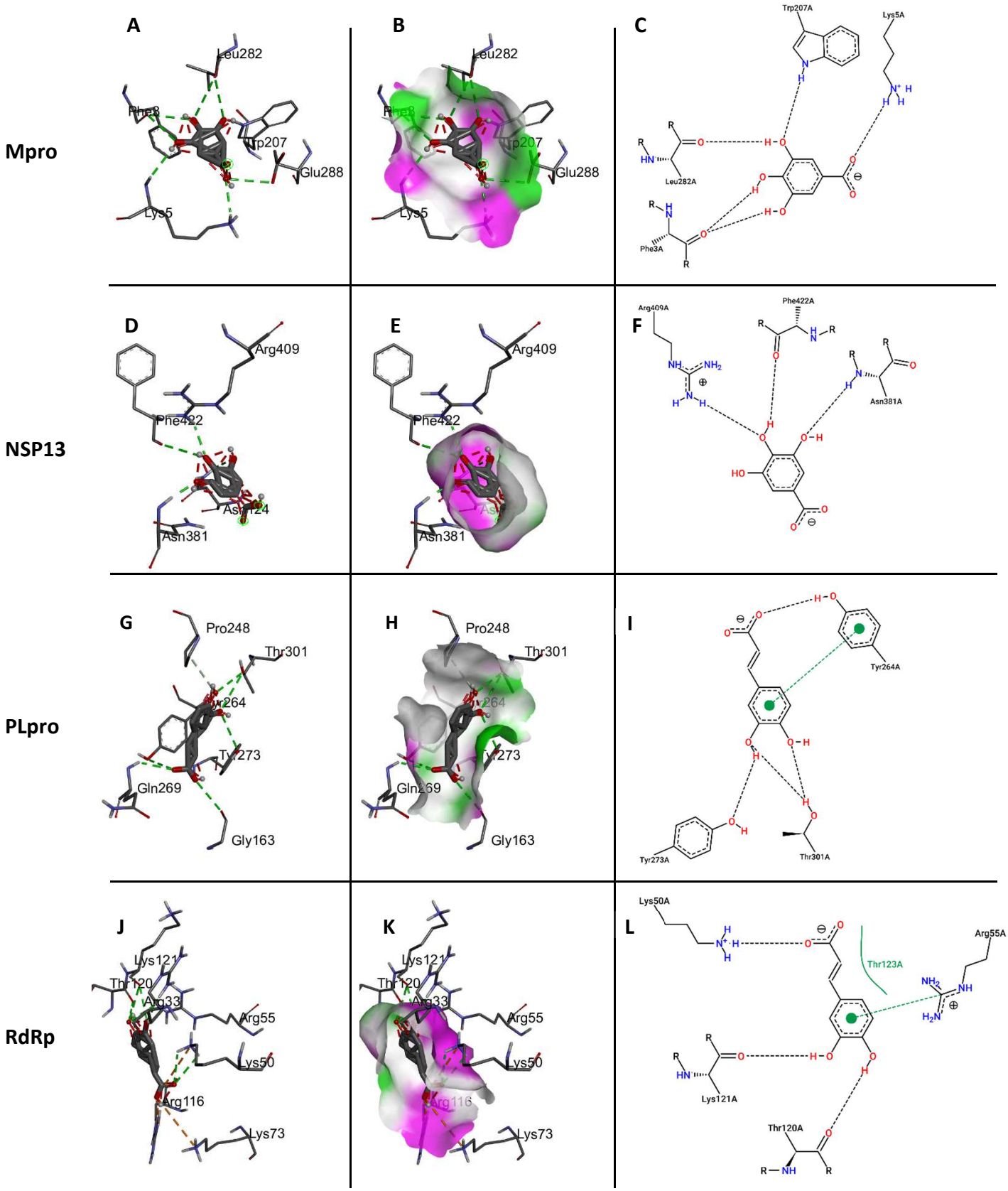

Fig. 2 Illustration of docking results between SARS-CoV-2 viral proteins and ligands

Illustration of docking between SARS-CoV-2 viral protein and ligands. (A, B) demonstrate the three-dimensional view of docking between gallic acid and main protease (Mpro) while two-dimensional view shown in (C). (D, E) illustrate the three-dimensional view docking between gallic acid and NSP13 whereas two-dimensional view shown in (F). Three-dimensional view of Caffeic acid and papain like protease (PLpro) interaction depict in (G-H) while two-dimensional view demonstrates in (I). Interaction between RNA dependent RNA polymerase (RdRp) and caffeic acid illustrate in (J-L). The conventional hydrogen bonds are denoted as black dashed line while pi-interaction (parallel) and pi-amide bonds are depicted in green dashed lines.

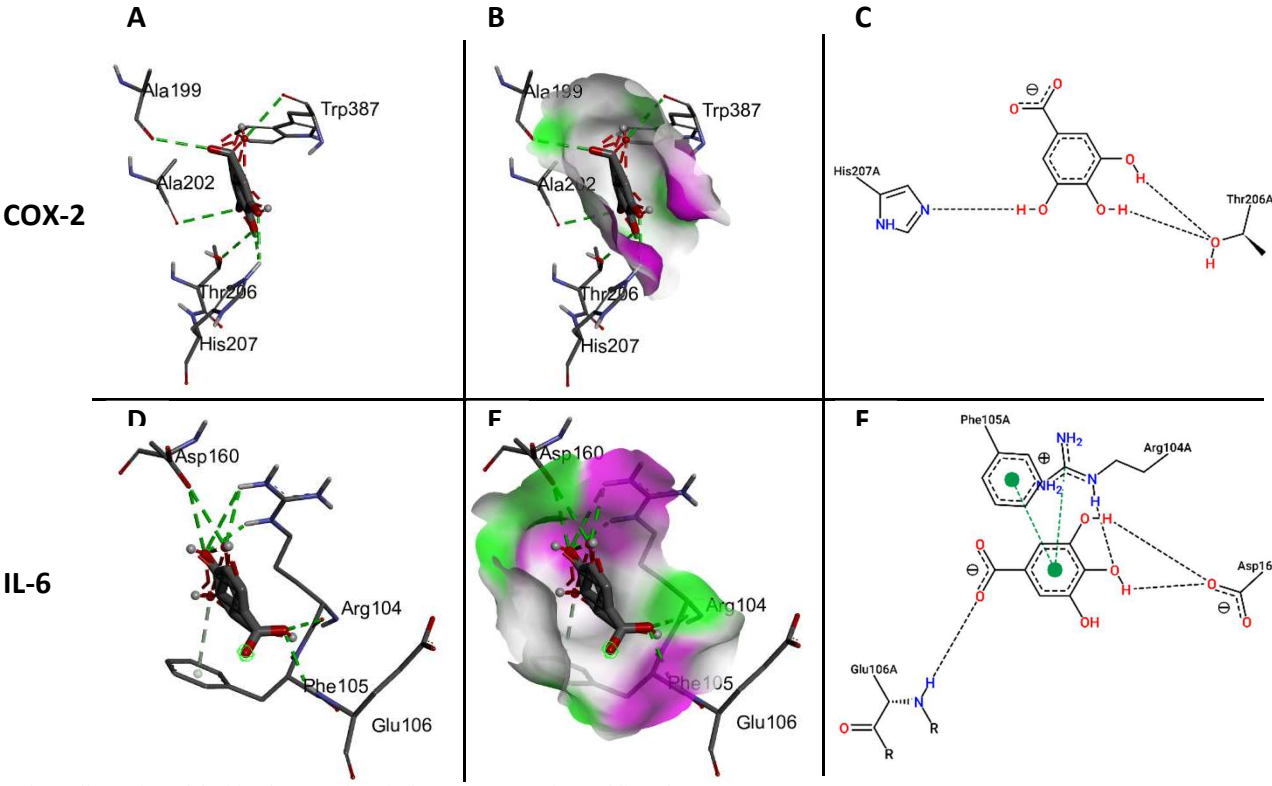

Fig. 3 Illustration of docking between host inflammatory proteins and ligands

Table 2 ILLUSTRATION OF LIPINSKI'S RULE OF FIVE TO DETERMINE DRUG-LIKENESS

Compound	MW (g/mol)	TPSA (Å2)	HB A	HB D	LogPo/w (iLOGP)
Limonene	136.23	0	0	0	2.27
Geraniol	154.25	20.23	1	1	2.52
Gamma-Terpinene	136.23	0	0	0	2.73
Geranyl Acetate	196.29	26.3	2	0	3.27
Caffeic Acid	180.16	77.76	4	3	0.97
Ferulic Acid	194.18	66.76	4	2	1.67
Gallic Acid	170.12	97.99	5	4	0.21

V. CONCLUSION

Collectively, our results suggest that natural compounds of coriander possess promising antiviral activity by inhibiting SARS-CoV-2 virus proteins that are essential for maintaining the virus life cycle. Furthermore, such compounds also exert anti-inflammatory activities by inhibiting host inflammatory proteins thereby perturbing the inflammatory pathways activated during SARS-CoV-2 infection. Further, ADMET analysis revealed that these two compounds could also be proposed as a potential natural drug molecule for the treatment of SARS-CoV-2. Nevertheless, we must confirm the results with wet-lab experiments.

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