Molecular docking prediction of carvone and trans-geraniol inhibitability towards SARS-CoV-2

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Submitted October 19, 2020; Revised January 20, 2021; Accepted May 10 2021

Abstract

Carvone and geraniol, well-known by their biological activity, could be promising natural inhibitors for angiotensin-converting enzyme 2 (UniProtKB-Q9BYF1), SARS-CoV-2 main protease (PDB-6LU7), and SARS-CoV-2 spike glycoprotein (PDB-6VSB). Quantum properties of R-(−)-carvone (CA1), S-(+)-carvone (CA2), and trans-geraniol (GE) were examined using density functional theory (DFT). Their inhibitability towards the targeted proteins was evaluated using molecular docking simulation. Lipinski's criteria were utilised to preliminarily screen drug-likeness of the potential inhibitors. Quantum analysis suggests that the compounds are highly favourable for intermolecular interaction towards protein structures. The overall inhibitability of the ligands follows the order GE > CA2 > CA1. Their biologically rigid conformation is given by RMSD registering under 2 Å in any systems. The expected inhibition is explainable by topographical complementarity between the inhibitory aducts. All the candidates are predicted compatible with pharmaceutical applications in physiological environments. Their high polarisability is also conducive to inhibitory activity towards highly polarised protein-structures. The study proposes carvone and geraniol to be promising for natural medication-assisted agents supporting treatment against infection caused by SARS-CoV-2.

Keywords. SARS-CoV-2, carvone, trans-geraniol, quantum analysis, docking simulation.

1. INTRODUCTION

SARS-CoV-2 is a new strain of a large family of human pathogens known as the name coronavirus, the well-known agents causing common colds in humans. The diseases include significantly severe ones such as the Middle East Respiratory Syndrome (MERS), Severe Acute Respiratory Syndrome (SARS) and Severe Acute Respiratory Syndrome coronavirus 2019 (COVID-19).[1,2] The lastest is causing the current severe pandemic worldwide, which is due to the infection by SARS-CoV-2. Therefore, demands for discovery of sufficient medicines or effective medication-assisted agents for treatment of the infection are of great and urgent concern to researches around the world.

SARS-CoV-2 infection is based upon a virus-host interaction of two proteins. First, angiotensin-converting enzyme 2 (ACE2) in human is an integral membrane glycoprotein, known for highest expression in tissues such as kidney, endothelium, lungs, and the heart.[3] However, it was speculated that the protein is the host receptor of the SARS-CoV-2 and SARS-CoV.[4] Therefore, if protein ACE2 can be temporarily inhibited, infection caused by SARS-CoV-2 to human would be deferred. ACE2 structural database (DOI: 10.2210/pdbACE2/pdb) can be referenced from UniProtKB (figure 1A). Second, SARS-CoV-2 main protease, functioning as a proteolytic enzyme cutting polyproteins into functional pieces,[5] was already well defined and archived at Worldwide Protein
Natural products, isolated from living organism, has been considered to be a valuable source for manufacture of medicines and drugs thanks to their bioactivities and physiocompatibility.[10-12] Their extensively availability in natural reservoir means that they can be either exploited directly by folk medicine or investigated for further development. The former is justified by the fact that natural products have been under rigorous natural selection in order to gain evolved value making up their existence. In addition, they are often reported more favourable to humans than their synthetic counterparts.[10] On the other hand, natural substances, especially newly indentified compounds, can serve as lead structures for preparation of their derivatives, which perform elevated efficacy or even novel properties. This is especially important for developing new antiviral agents.[13] Zanamivir, peramivir, and lanamivir octanoate are typical examples for antiviral drugs successfully developed from natural product-derived compounds.[14]

Carvone chemotypes and geraniol, which are originated from nature could be considered as promising candidates for medical applications at cytological scales. Carvone is primarily extracted and purified from essential oils of caraway, dill, and spearmint seeds; meanwhile, its synthetic products can be produced by either chemical or biotechnological methods. Dill seeds have ca. 40-60 % of their essential oils composing of carvone. The main constituents of caraway seeds are S-(+)-carvone (50-70 %) and (+)-limonene (25-30 %). Meanwhile, R-(−)-carvone can be extracted from spearmint, a Mediterranean-native plant.[15] Carvone was well demostrated exhibiting both antibacterial and antifungal activity, effective against a wide spectrum of pathogenic fungi and bacteria.[15-19] The cytotoxicity and genotoxicity of the chemotype were also reported by Stammati et al.[20] Regarding cytological interaction, the results showed that carvone inhibited viability and proliferation of Hep-2 cells in a dose-dependent manner. In terms of genetic activity, carvone caused no damage in DNA structures at a certain dose. "Geraniol" is a natural product common name referred to two cis-trans isomers, whose names are geraniol (trans) and nerol (cis). The former was mainly isolated from Palmarosa oil while the latter was obtained from...
neroli essential oils.\textsuperscript{[21,22]} Specifically, geraniol is well-known exhibiting a variety of biochemical and pharmacological properties. These include plant-based insect repelling,\textsuperscript{[23]} antimicrobial,\textsuperscript{[24]} and antitumoural activities. The latest is against murine leukemia,\textsuperscript{[25]} hepatoma and melanoma cells.\textsuperscript{[26,27]} Besides, neither mutagenic effects nor significant toxicity of the substance have been observed in various thorough studies.\textsuperscript{[28-30]} The structural formula of the investigated compounds are shown in figure 2.

Silico technique for medical science is currently seeing a gain of their popularity since it can reduce cost and time of laboratory experiments significantly. In detail, the approach is based on computational simulation and computing calculation as prescreening research, predicting the compounds with undesirable properties and the most promising candidates. The former substances are eliminated while the latter justifies the next analysis or further developed research.\textsuperscript{[31]} Regarding ligand-protein interaction, molecular docking simulation is an effective method to investigate the potency of a ligand as an inhibitor towards its targeted protein by estimating ligand-target binding energy and static stability of the inhibitory systems.\textsuperscript{[32]} The evaluation also includes details on intermolecular interaction.

In this study, the inhibitiability of R-(−)-carvone (CA1), S-(+)-carvone (CA2), and trans-geraniol (GE) towards SARS-CoV-2-related proteins (ACE2, 6LU7, and 6VSB) is investigated. The ligand quantum properties were determined by DFT modelling. The results include their optimised structure and molecular orbital configuration. The inhibitiability was examined via molecular docking simulation. Finally, their physiochemical and pharmaceutical compatibility was evaluated based on Lipinski's criteria. Desirable results are justified by their significance towards the prevention of SARS-CoV-2 infection. To the best of our knowledge, to date, there is no report on the activities of of R-(−)-carvone, S-(+)-carvone, and trans-geraniol against SARS-CoV-2 via inhibition of angiotensin-converting enzyme 2, SARS-CoV-2 main protease 6LU7, and SARS-CoV-2 spike glycoprotein 6VSB.

2. COMPUTATIONAL METHODS

2.1. Quantum chemical calculation

Molecular quantum properties of the investigated compounds (CA1, CA2, and GE) and their optimised geometry were examined by density functional theory (DFT) using Gaussian 09 without symmetry constraints\textsuperscript{[33]} at level of theory M052X/6-311++G(d,p).\textsuperscript{[34]} Structural global minimum on the potential energy surface (PES) was confirmed by calculation of vibrational frequencies on the respective molecules. The frozen-core approximation for non-valence-shell electrons with calculation using a larger basis set def2-TZVPP\textsuperscript{[35]} yielded single-point energies at the M052X/6-311++G(d,p)-level-optimised geometries.

Resolution-of-identity (RI) approximation was applied for each optimisation run. NBO 5.1 available in Gaussian 09 was utilised frontier orbital analysis at level of theory BP86/def2-TZVPP\textsuperscript{[35]}, which provided information of molecular electron density distribution and molecular orbital energy. The highest occupied molecular orbital (HOMO) energy, \( E_{HOMO} \), represents intermolecular electron donation tendency; meanwhile, electron-accepting ability of a molecule can be inferred from its value \( E_{LUMO} \) (for lowest unoccupied molecular orbital - LUMO). By exhibiting molecular electronic excitability, energy gap \( \Delta E = E_{LUMO} - E_{HOMO} \) can suggest intermolecular reactivity of the host molecule.
2.2. Molecular docking simulation

Ligand-protein interactability was computationally simulated using MOE 2015.10. The results included intermolecular-complex configurations, docking score (DS) energy, root-mean-square deviation (RMSD), types of interactions, and respective distances between the potential drugs and proteins. In a typical procedure, molecular docking simulation follow three steps.\textsuperscript{[37-40]}

1) Pre-docking preparation: Structural information of the targeted proteins can be referenced at UniProtKB and Worldwide Protein Data Bank: angiotensin-converting enzyme 2 (entry: UniProtKB - Q9BYF1), SARS-CoV-2 main protease 6LU7 (DOI: 10.2210/pdb6LU7/pdb), and SARS-CoV-2 spike glycoprotein 6VSB (DOI: 10.2210/pdb6VSB/pdb). Their 3D-protonation structures were prepared by Quickprep tool, while their active zones were determined based on the ligand position within a radius of 4.5 Å and the presence of important amino acids. The achieved structures were saved in *.pdb format. Independently, the ligand structures, i.e. CA1, CA2, and GE, were optimized based up the configuration: Conj Grad for minima energy; termination for energy change = 0.0001 kcal.mol\(^{-1}\); max interactions = 1000; modify charge: Gasteiger-Huckel.

2) Docking investigation: After preparation for input, intermolecular interaction simulation was performed on MOE 2015.10 system under the configuration: poses retaining for intermolecular interaction probing = 10; maximum solutions per iteration = 1000; maximum solutions per fragmentation = 200. The simulated ligand-protein inhibitory structures were saved in format *.sdf.

3) Post-docking analysis: Docking score (DS) energy indicates Gibbs free energy of the respective ligand-protein inhibitory system, thus considered as the primary indicator of the duo-system inhabitation. Intermolecular interactions formed between the ligands and in-pose amino acids of the proteins include hydrophilic binding, e.g. electron-transferring (H-acceptor/donor), cation-arene (H- π), arene-arene (π- π), and ionic and hydrophobic interaction, aka. van der Waals forces. The simulation results in-bonding amino acids, bonding lengths, and their Gibbs free energy in regard of these interactions. A root-mean-square deviation (RMSD) value predicts static conformation of an inhibitory complex as it represents the average between neighbouring atoms. Therefore, a smaller value means a more tightly bound conformation is formed. In addition, in-pose arrangement of the ligands were visualised on 2D and 3D planes.

2.3. Physicochemical and pharmaceutical compatibility

The docking parameters including DS\textsubscript{average} (kcal.mol\(^{-1}\)), molecular mass (Da), polarizability (Å\(^2\)), size (Å), and dispersion coefficients (logP and logS) were achieved using QSARIS system by Gasteiger-Marsili method.\textsuperscript{[32]} A prescreening was implemented in order to evaluate their orally pharmacological compatibility based on Lipinski’s rule of five, a well-known set of indicators to predict drug-likeness.\textsuperscript{[41]} According to Lipinski’s criteria, a well membrane-permeable molecule should satisfy the requirements: (1) Molecular mass < 500 Da; (2) no more than 5 groups for hydrogen bonds; (3) no more than 10 groups receiving hydrogen bonds; (4) the value of logP is less than +5 (logP < 5).\textsuperscript{[42,43]}

3. RESULTS AND DISCUSSION

3.1. Quantum chemical property

Geometrically optimised structure of the studied compounds (CA1, CA2, and GE) are shown in figure 3, their frontier molecular orbitals (HOMO and LUMO) are presented in figure 4, and the related quantum parameters are summarised in Table 1. Firstly, it is noticeable that each compound contains a polarised carbonyl group (C=O), thus conducive to their solubility in physiological mediums. Also, there is no abnormal parameter observed from the quantum analysis regarding either bond length or bonding angle. The former registers ca. 1.3-1.5 Å for C-C bonds and ca. 1.2-1.4 Å for C=O bonds, while the latter includes the values of ca. 107-108° at \(sp^3\)-hybridised atoms and ca. 117-120° at \(sp^3\)-hybridised atoms. These are prevalently acknowledged in the literature. Regarding configuration of their frontier molecular orbitals, CA1, CA2, and GE are suggested performing desirable intermolecular interaction. In fact, their HOMO and LUMO electron density are evenly distributed and largely space-occupied over the molecular planes, thereby varifying inhabitable approaching manners as the molecules can execute
electron-transferring flexibly. The significance of their electronegativity (over 4) also suggests that CA1, CA2, and GE all exhibit highly electron-attracting tendencies, in turn upholding their external inhibition. In particular, energy gap ($\Delta E_{\text{GAP}}$) of CA1, CA2, and GE are 8.082, 8.146, and 7.320 eV, respectively, suggesting the latest as the most quantum-favourable candidates for intermolecular activities. The reasoning is due to the ease for its molecular electrons to be activated.\textsuperscript{[44-46]} Therefore, the compounds seem preliminarily promising for docking investigation.

![Figure 3: Optimized structures of investigated compounds CA1, CA2 and GE calculated by DFT at level of theory M052X/6-311++g(d,p)](image)

![Figure 4: HOMO and LUMO of the investigated compounds CA1, CA2, and GE calculated by DFT at level of theory M052X/def2-TZVP](image)

**Table 1:** Quantum chemical parameters of the compounds CA1, CA2, and GE calculated by NBO analysis at level BP86/def2-TZVP including HOMO energy ($E_{\text{HOMO}}$), LUMO energy ($E_{\text{LUMO}}$), energy gap ($\Delta E_{\text{GAP}}$); ionization potential ($I$); electron affinity ($A$); electronegativity ($\chi$), chemical potential ($\mu$)

| Parameter                        | CA1  | CA2  | GE   |
|----------------------------------|------|------|------|
| $E_{\text{HOMO}}$ (eV)           | -8.463 | -8.599 | -7.919 |
| $E_{\text{LUMO}}$ (eV)           | -0.381 | -0.435 | -0.599 |
| $\Delta E_{\text{GAP}} = E_{\text{LUMO}} - E_{\text{HOMO}}$ | 8.082 | 8.146 | 7.320 |
| $I = -E_{\text{HOMO}}$          | 8.463 | 8.599 | 7.919 |
| $A = -E_{\text{LUMO}}$          | 0.381 | 0.435 | 0.599 |
| $\chi = (I + A)/2$              | 4.422 | 4.517 | 4.259 |
| $\mu = -\chi = -(\partial E/\partial N)_{\text{H2O}}$ | -4.422 | -4.517 | -4.259 |

3.2. Molecular docking inhibitory

Detailed parameters for inhibitory duos are summarised in table 2, which reveal the order of overall inhibitory ability of the inhibitory ligands regardless of their targeted proteins, i.e. GE > CA2 > CA1. All compounds are highly promising inhibition of all studied proteins given their significant DS values. In fact, GE-protein inhibitory complexes are likely most stable given their dominant DS values: -15.4 (GE-ACE2), -17.1 (GE-6LU7), and -14.2 (GE-6VSB) kcal.mol\textsuperscript{-1}. Their significance is justified by comparison to the corresponding values derived from the two commercially approved drugs (ribavirin and remdesivir), ca. 16-17 kcal.mol\textsuperscript{-1}, in resembling simulations.\textsuperscript{[45]} Respectively, these are followed by those of CA2-protein systems, which are -14.1
CA2-ACE2, -14.4 (CA2-6LU7), and -13.7 kcal.mol\(^{-1}\)(CA2-6VSB). Although performing rather ligand-protein inhibitorily desirable DS value in comparison to resemble researches in the literature,\(^{[47-49]}\) no DS value standing lower than -13.5 kcal.mol\(^{-1}\) indicates that CA1 expects least promising amongst the selective candidates in this study for SARS-CoV-2 inhibition-based treatment. All RMSD values are under 2 Å, implying that the structures are predicted biologically rigid. Significantly, CA1-ACE2, CA2-6LU7, and GE-6LU7 expect forming ligand-bound conformations given the short average distance between their internal neighbouring atoms (< 1 Å).\(^{[49]}\) Nevertheless, their inhibitory capacity is unlikely stemmed from direct chemical interactions. Most inhibitor adducts are bound by 1-2 hydrogen bonds; while, their hydrophobic binding is also established based on ca. ten van de Walls interactions for each inhibitory system.

**Table 2: Molecular docking simulation results regarding inhibitory complexes: ligand-ACE2, ligand-6LU7 and ligand-6VSB**

| Ligand-protein complex | Hydrogen bond | van der Waals interaction |
|-----------------------|---------------|--------------------------|
| Name                  | DS  | RMSD | L | P | T | D | E |
| CA1-ACE2              | -13.4 | 0.68 | O | N | Lys 291 | H acceptor | 3.09 | -1.4 |
| CA2-ACE2              | -14.1 | 1.60 | O | N | Gln 301 | H acceptor | 3.13 | -2.1 |
| GE-ACE2               | -15.4 | 1.47 | O | N | Gln 301 | H acceptor | 3.23 | -0.5 |
| CA1-6LU7              | -12.9 | 1.49 | O | S | Met 165 | H donor | 3.85 | -0.3 |
| CA2-6LU7              | -14.4 | 0.70 | O | N | Gln 189 | H acceptor | 2.90 | -3.8 |
| GE-6LU7               | -17.1 | 0.87 | C | 5-ring | His 41 | Hπ | 4.24 | -0.7 |
| CA1-6VSB              | -13.4 | 1.41 | C | N | Gln 1036 | H acceptor | 2.98 | -3.0 |
| CA2-6VSB              | -13.7 | 1.85 | C | N | Gly 1093 | H acceptor | 2.91 | -1.4 |
| GE-6VSB               | -14.2 | 1.48 | O | N | Cys 1043 | H acceptor | 3.02 | -2.7 |

DS: Docking score energy (kcal.mol\(^{-1}\)); RMSD: Root-mean-square deviation (Å).
L: Ligand; P: Protein; T: Type; D: Distance (Å); E: Energy (kcal.mol\(^{-1}\)).

The inhibitory structures are visually illustrated in figure 5. The flexibility of *trans*-geraniol molecule (GE) is explicit as it is highly transformable in accordance with the targeted-protein active sites. This reasons its elevated inhibitability in comparison to the carvone counterparts. Moreover, almost entirely continuous proximity contour indicates that all ligands are in significant complementarity with the topography of their inhibiting site. Such topographical
complementarity might compensate for lack of chemical interaction, hence significance of total Gibbs free energy (DS value) retaining. Also, mobility of the ligands given by small molecular structure is likely conducive to their active-site entry, thus stable configuration (represented by low DS value) ensuing. Finally, observation on 3D models reinforces the inhibitability of the ligands as all inhibited sites are still spacious for either simultaneous entry or in-pose conformational orientation.

Figure 5: Visual presentation and in-pose interaction map of ligand-ACE2, ligand-6LU7, and ligand-6VSB inhibitory complexes: (A) CA1-ACE2, (B) CA2-ACE2, (C) GE-ACE2, (D) CA1-6LU7, (E) CA2-6LU7, (F) GE-6LU7, (G) CA1-6VSB, (H) CA2-6VSB, (I) GE-6VSB
3.3. Physiochemical and pharmaceutical compatibility

Table 3 summarises several properties of CA1, CA2, and GE for screening their physicochemical and pharmaceutical compatibility in reference to Lipinski's criteria. The rule suggests that a molecule with good membrane permeability should have LogP ≤ 5, molecular weight ≤ 500 amu, the number of hydrogen bond acceptors ≤ 10, the number of hydrogen bond donors ≤ 5. They are thoroughly met by every investigated compound. Besides, their polarisability is 18.2, 18.9, and 20.1 Å³, respectively. Such significant polarisation is thought markedly conducive to protein inhibition as the polypeptides are constructed by polarised amino acids. In addition, their QSARIS-based size are measured under 300 Å.

Table 3: Summarisation of physiochemical properties of studied compounds including docking score energy values (DS, kcal.mol⁻¹), molecular mass (M, amu), polarizability (Å³), volume or size (Å), logP, logS and the total of hydrogen bonds of potential substances CA1, CA2, GE docked with the three proteins ACE2, 6LU7, and 6VS

| Parameter                  | CA1  | CA2  | GE   |
|----------------------------|------|------|------|
| DS average (kcal.mol⁻¹)    | -13.2| -14.1| -15.6|
| Mass (amu)                 | 150.2| 150.2| 154.3|
| Polarisability (Å³)        | 18.2 | 18.9 | 20.1 |
| Volume (Å)                | 265.3| 265.3| 295.8|
| Dispersion coefficients LogP | 1.68 | 1.68 | 2.57 |
|                           | LogS | -1.87| -1.90|
| Total of hydrogen bond     | 3    | 3    | 5    |

In summary, CA1, CA2, and GE are highly proposed as temporary inhibitors of angiotensin-converting enzyme 2, SARS-CoV-2 main protease 6LU7, and SARS-CoV-2 spike glycoprotein 6VSB. This is more likely based on their topographical complementarity than depended upon chemical interactions. Their drug likeness is preliminarily satisfied in consideration to Lipinski's rule of five. Therefore, further attempts for experiment-based confirmation are justifiable.

4. CONCLUSION

This study opens a promising approach to the use of R-(−)-carvone (CA1), S-(+)-carvone (CA2), and trans-geraniol (GE) serving as multi-inhibitors targeting at proteins ACE2, 6LU7, and 6SVB. Quantum properties of the ligand molecule suggest favourableness for intermolecular activity in general and inhibition towards protein structures in particular. The overall inhibitability of the potential inhibitors accords with the order GE > CA2 > CA1 by primary justification based on DS values of the inhibitory complexes. Their conformations expect biologically ligand-bound given their RMSD under 2 Å. Lipinski's rule of five preliminarily validates their promising applicability in pharmaceutical and physiological mediums. All compounds possess significant polarisability, which is deemed suitable for interaction with polarised protein structures. The results are considered highly conducive to exploit of natural medication-assisted agents supporting therapeutic treatment for SARS-CoV-2 infection.

Acknowledgement. This research is supported by the Vietnam National Foundation for Science and Technology Development (NAFOSTED) under grant number 02/2020/DX. Nguyen Thi Ai Nhung acknowledges the partial support of Hue University under the Core Research Program, Grant No. NCM.DHH.2020.04.

Conflict of interest. The authors declare no conflict of interest.

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