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A Molecular Modelling Approach of Some Keto-Based Natural Drugs with Potent Antiviral Activity Towards SARS-Cov-2

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ABSTRACT

COVID-19, produced by SARS-CoV-2 has just inaugurated as a global pandemic. Intense efforts are also underway to discover a drug or vaccine across the globe to resist the outbreak. Nowadays, alternative treatments for the management of the disease are also being explored. It has been proven that phytochemicals from various plant extract are the promising candidate in dealing many therapeutic activities with minimum side effects. Herein, this article will cover the major uses of keto based natural drugs such as pulegone, camphor, thymoquinone for their antimicrobial properties against the proteases of receptor binding domain, which is one of the vital targets for novel antiviral agents. In order to discover the new possible COVID-19 inhibitors, the proteases PDBs e.g., 2gtb and 6lu7 will be used as hosts to calculate the interactions with those aforementioned natural drugs as guests. Those protein compounds are chosen because they share 96% similarity of antiviral nature. A comprehensive molecular docking approach (through both Auto dock and CCDC GOLD) have been introduced for the theoretical calculations of binding energies as a result of host-guest interactions. Furthermore, protein ligand interaction profiler (PLIP) server also provides hydrophobic interactions (clear data about amino acid residues along with bond distances), 3D view of molecules, number of hydrogen bonds, etc. Present research shows that pulegone is the most active having binding energy -5.93 kcal/ mol against 2gtb viral spike-protein, whereas, on the other, that of camphor is -4.92 kcal/ mol against 6lu7 protease of SARS-CoV-2.

INTRODUCTION

In the late 2019, an infection in Wuhan city of Hubei, China was identified from a tainted human, which was subsequently known as severe acute respiratory syndrome (SARS) Corona virus2i.e., SARS-CoV-2 [1,2]. This infection is a contaminated illness related with human-to-human transmission influencing the respiratory framework as well as influence the stomach related problems fundamentally [3]. Till February 2021, there are 112,456,453 affirmed cases and 2,497,514 passing around the world. America and Europe are worstly influenced alongside India, with millions of cases. Pacific, Asia and African nations are additionally lethally influenced [4].

Scientists are continuously working for the improvement of immunization and medications to treat COVID-19. Also, Food and Drug Administration (FDA) redeployed affirmed drugs for the adequacy against SARS-CoV-2. One next to the other plant-based therapies are additionally explored to fix or dealt with the illnesses. Despite the fact that in west nations, manufacturing mixtures are being utilized in the last decade, where regular Phyto-compounds are likewise under research. Moreover, bioactive Phyto-intensifies which were generally utilized, have now become vital medications to treat viral illnesses. There is an assorted combination of natural mixtures overwhelmingly made out of terpenes, terpenoids, phenylpropanoids, and aldehydes [5-7]. Distinctive normally happening natural keto-intensifies shows antimicrobial, antibacterial, and antiviral properties.

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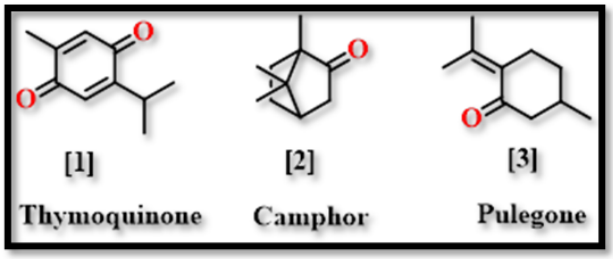
Hence, natural mixtures based remedial methodology can be focused, which are composed of organic compounds having hydroxyl and keto groups. Past investigations show that numerous fundamental mixtures, where the major counterpart is hydroxyl functional group based organic ligands, have been successful in hindering attack of microorganisms. With regards to this investigation identified with antiviral properties, a couple of fundamentals organic ligands have been viable against RNA and DNA infections, for example, avian fluan infection [8], herpes simplex infection type 1 (HSV-1) and type 2 (HSV-2), dengue infection type 2, Junín infection, flu infection adenovirus type 3, poliovirus, and coxsackievirus B1 [9].

Since there is a limited number of a medication accessible for treating viral illnesses, specific understanding towards drug developments thus unmet need of current research. To evaluate the restorative capability of specific drug, it is fundamental for knowing the association between the ligands and the protein at sub-atomic level. An underlying *in- silico* study including numerous methods impressively can decreases the time required for this drug discovery processes [10-12]. Through computational investigation, it is too easy to find out viable outcomes about protein-ligand or host-guest interactions by analyzing some specific parameters, which can help further in targeted drug designing.

In persistence our recent advancements on biological effort on antimicrobial [13-16], anticancer [13,17-20], bioinspired catalysis [18,21-24] and host-guest bio-conjugative studies [17,18,25-28], our emphasis of this article will be the discovery of some outstanding antiviral drugs though *in silico* techniques. Thus, in this report, we have chosenSARS-CoV-2 principle protease as host for situation with some keto-based naturally available organic ligands [29,30]. The protease receptor proteins via 2gtb and 6lu7 have been selected as these are answerable for the combination of viral effect with 96% similarity and cellular imbalance in our body [31,32]. Moreover, keto-based ligands are yet not explored much *via* theoretical simulation in comparison to hydroxy analogous. Therefore, in the current examination, molecular docking and the applied density functional theory (DFT) [13,15,18,24,26-28] approach have been used to evaluate the antiviral properties of significant segments of certain fundamental natural keto-based drugs extracted from various plants that are outstanding for antimicrobial action. Using molecular docking, hydrogen bonding and hydrophobic connections have been checked properly in the stable collaboration between the protein and ligand **(Scheme 1)**.



Scheme 1. Chosen keto-based characteristics medication as SARS-CoV-2 objective.

MATERIALS AND METHODS

Selection and preparation of host protein structure

The protease subunit of SARS-CoV-2 proteins such as PDB ID: 6lu7 and PDB ID: 2gtb were particularly chosen as the target with selected ligand molecules. The reason behind the selection of protease subunit is because of its strong contribution towards viral effect. Those host proteins were downloaded from the RCSB protein data bank in pdb format. Pymol was then used for visualizing 3D structure followed by the removal of water molecules and unwanted species bounded to the host pdb. After successful generation of pdb host from Pymol, Autodock software was taken for adjusting various charges and energies associated with the pdb of hosts. Rather pdb was converted to pdbqt format using the same software for further uses [33,34].

Selection and preparation of ligands

We have taken three keto compounds as ligands viz thymoquinone, camphor and pulegone. These ligands along with their hydroxyl analogues are known for its antiviral, and/ or anti-bacterial activities. These are selected as guests against the SARS-CoV-2 protease-based hosts *viz;* 2gtb and 6lu7. Now, ChemDraw3D along with MM2 performance has been used to generate each structure of ligand for finding out the detail information about their exact chemical composition. The exported pdb of the ligands from ChemDraw further used to calculate the geometry optimized structure through density functional theory (DFT). These ligands were screened at Auto dock software which converts pdb files into pdbqt format. This process involves detecting torsion root, adjusting torsion angle assigning charges and changing them to pdbqt format for their further use during molecular docking [13,18,35].

Theoretical calculations of ligand structures

Density functional theory (DFT) gives us an idea of solid-state structure of a molecule using the quantum formulations [36]. Another field of DFT is to state about chemical behavior by using electron density calculation. In order to achieve the geometry optimized structures, Gaussian09 programme having B3LYP basis set and 6-31G(+)d,p functional have been used for each ligand. Furthermore, different parameters have been elucidated via DFT

calculations, which includes total energy, molecular dipole moment, lowest unoccupied molecular orbital (LUMO) and highest occupied molecular orbital (HOMO) energies, band gap (ΔE), absolute hardness (η), fraction of electrons transfer (ΔN), and electro negativity (χ) [16].

Molecular docking

In-silico technique anticipate suitable interconnection between protein molecules of hosts and small guests (*viz.* ligand) based on their geometry and structure [37]. In this report, molecular docking is performed by using certain software and servers such as Autodock, CCDC Gold, PLIP, Open Bable GUI, Chimera, and Protein. Plus.

In Autodock, the accuracy and speed are maintained throughout the steps. The protein and the ligand molecules were selected with little adjustment of Kollman, and residual charges. Apart from that the structure is dehydrated and hetero atom(s) were deleted wherever applicable. Furthermore, torsion tree grid and spacing were set followed by running 'auto grid' and 'auto dock' programmes to get the host-guest interaction based docked results in the form of binding energy and inhibition constant [38].

The best dock pdb file obtained in Autodock were selected and converted to pdbqt format in open bable tool. The cavity site recognition is known to be preliminary step for protein binding site recognition was done through protein plus server and the 3D structure of molecules was observed through PLIP server.

Besides, CCDC Gold work proceeded by choosing HERMES tool, in which protein in pdb format is loaded followed by defining binding sites. Mol2 file of ligand prepared from CCDC Mercury, was selected by using ligand flexibility, GA setting, scoring function and all other required functions to run programme, which after completion gives docking solutions/ poses.

Chimera is an extensible program for instinctive portrayal and examination of nuclear developments and related data, including thickness maps, supra molecular social occasions, gathering game plans, docking results, bearings, and conformational outfits. Structural analysis is done using this, all the residues were also named using name specifier option. At last interaction poses and session were saved for further use.

RESULTS AND DISCUSSION

Molecular Docking

Docking technique is an *in-silico* technique, where the measurement of binding energy parameters and scores are used to predict how a protein interacts with ligands [39-41]. To identify potential antiviral activity, all the ligands taken are docked against host SARS-CoV-2 proteins. In this case docking result shows that pulegone gives the lowest value of binding energy (-5.93 kcal/ mol) during complexation with 2gtb and it is the best score as compared to other docked outcomes. The binding energy in case of thymoquinone (-5.78 kcal/ mol) as well as camphor (-5.70 kcal/ mol) is lower than that of pulegone. One hydrogen bonding interaction with amino acid GLN192 (H-donor) and three hydrophobic interactions *via* amino acid residues LEU167, PRO168, GLN192 are shown by pulegone in complexation with the host 2gtb. The hydrogen bonding and hydrophobic interaction between the ligand and the protein 2gtb are summarized in **Table 1**.

Docking results with PDB ID 6lu7 display that camphor gives best score (-4.92 kcal/ mol) than that of pulegone with -4.72 kcal/ mol, which is better than that of thymoquinone (-4.54 kcal/ mol). A strong hydrogen bonding interaction with amino acid TRP207 (H-donor) along with four hydrophobic interactions with amino acid residues PHE3, LYS5, PHE291, and PHE291 are shown by camphor against host 6lu7 protease of SARS-CoV-2. In the formation process of protein-ligand complexes, hydrogen bonding plays a vital role in determining its specificity and affinity of complexes. Hydrogen bonding and hydrophobic interactions play an important role in giving shape and stabilizing the docked complex. Apart from describing binding energy, comparison of inhibition constant (Ki) can also give the information about inhibitor potential. Here, pulegone with 2gtb shows best Ki value of 45.30 µM in comparison to thymoquinone (57.70 µM) and camphor (66.18 µM). On the other, in case of 6lu7 target, camphor has the least value of inhibitory concentration of 247.69 µM, which is better than that of pulegone (347.49 µM) and thymoquinone (493.47 µM). The hydrogen bonding and hydrophobic interaction between the selected keto-based ligands and the host 6lu7 are summarized in **Table 1.** The 3D binding poses, which is elucidated using Protein-Ligand Interaction Profiler (PLIP) server, and further visualised via ligplot tool to determine the 2D structure for more simplification **(Figure 1)**.

Furthermore, the docked ligands with hydrophobic interactions that are selected for identifying suitable binding pocket(s) around the ligands are summarized via Protein. Plus, server. This hydrophobic interaction between the ligands and the protein of host gives the information about the stability of the docked complex. The binding pocket of each ligand is shown in **Figure 2**, where different colors have been used for better visualization and easy investigation. PLIP outcomes are summarized in **Figure 3**, which provide not only the 3D plot but also the data related to hydrophobic interaction, amino acid involved in the interaction, and residue of that specific amino acid. Apart from that, hydrogen bonding and hydrophobic interactions plays an important role in giving shape and stabilizing the docking complex. From the results, it can be concluded that the number of hydrogen bonds as well as hydrophobic interactions are proportional to the activity of the corresponding ligand.

Table 1. Obtained scores from docking of ligand thymoquinone, camphor and pulegone with host protein 2gtb and 6lu7 of SARS-CoV- 2 virus.

Ligand	Protein of Host	RMSD*	Binding energy (kcal/mol)	Inhibition constant (ki)	No of H-bonds (drug-protein)	Amino acid involved in interaction	No of Hydro-phobic bond	Amino acid residue involved
Thymoquinone	2gtb	0.31	-5.78	57.70 µM	1	GLN192	5	LEU167, LEU167, PHE185, PHE185, GLA192
Camphor		0.03	-5.70	66.18 µM	3	GLY143, SER144, CYS145	1	ASN142
Pulegone		0.09	-5.93	45.30 µM	1	GLN192	3	LEU167, PRO168, GLN192
Thymoquinone	6lu7	0.22	-4.51	493.47 µM	1	LEU287	4	TYR239, LEU271, LEU272, LEU287
Camphor		0.08	-4.92	247.69 µM	1	TRP207	4	PHE3, LYS5, PHE291, PHE291
Pulegone		0.09	-4.72	347.49 µM	3	GLY143, SER144, CYS145	1	PHE140

**RMSD value of the best docked conformation.*

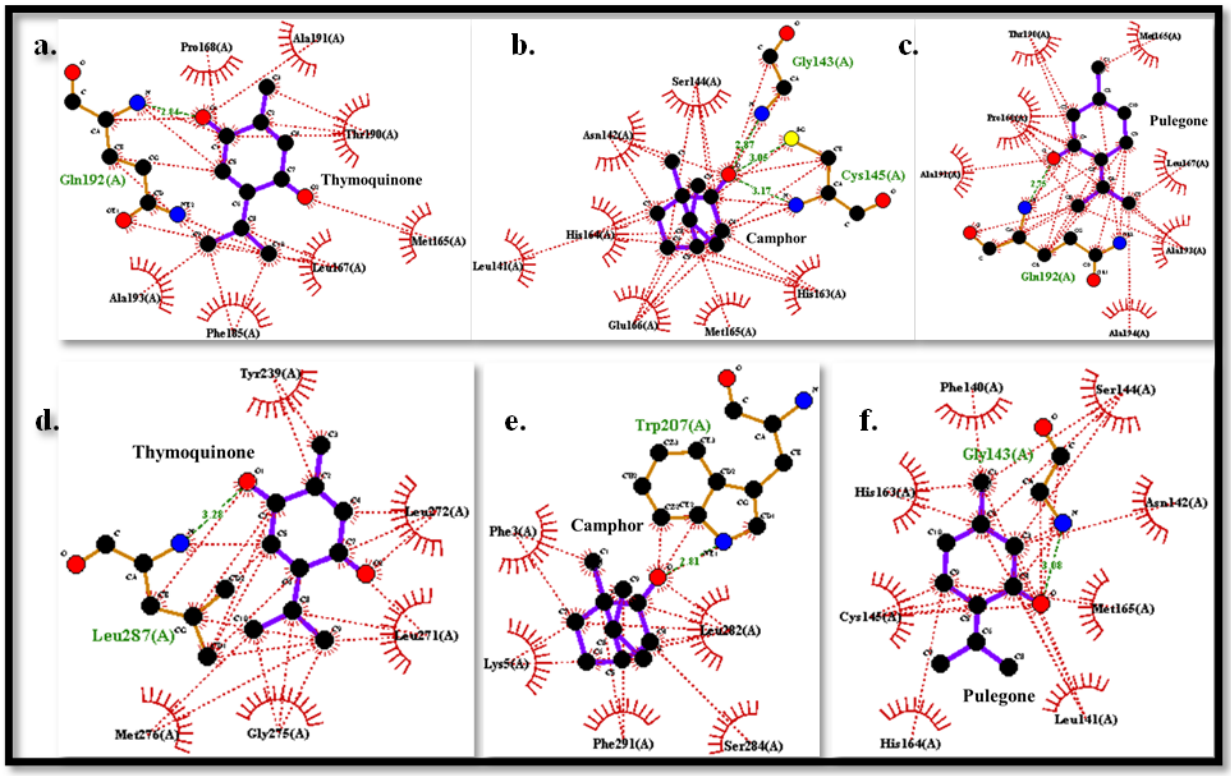


Figure 1. Comparative analysis of interaction between SARS-CoV-2proteins and natural keto-based natural drugs: (a) 2gtb-Thymoquinone, (b) 2gtb-Camphor, (c) 2gtb-Pulegone, (d) 6lu7-Thymoquinone, (e) 6lu7-Camphor, and (f) 6lu7-pulegone.

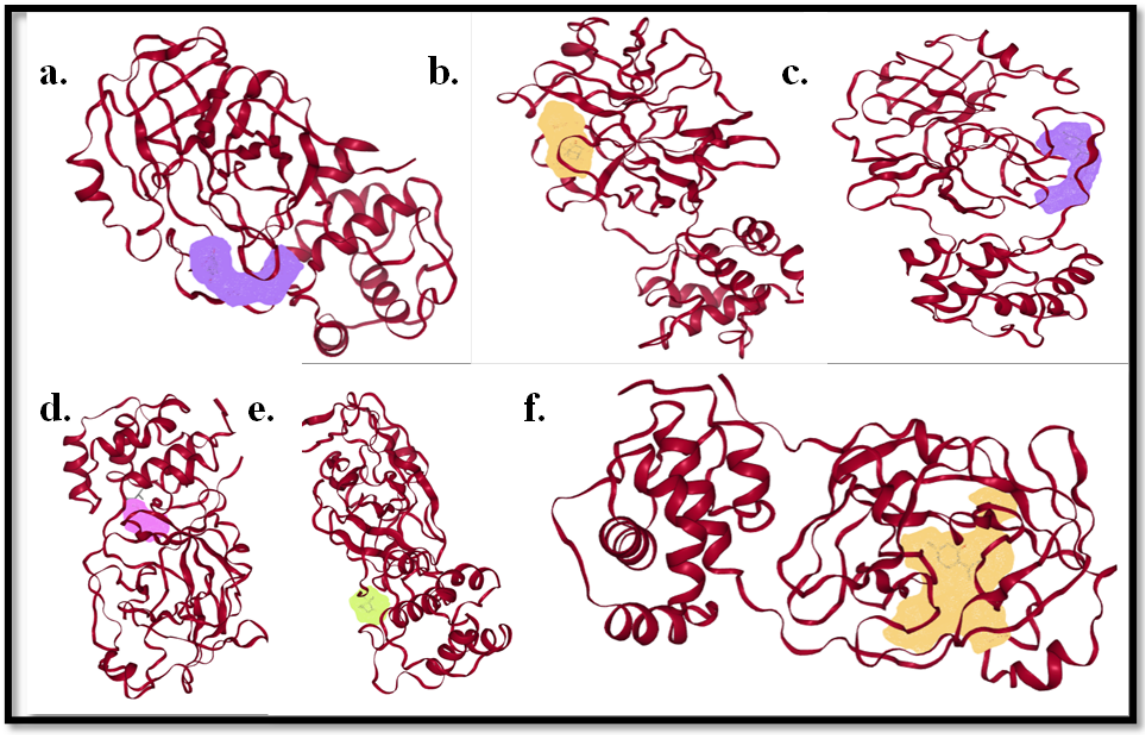


Figure 2. Binding Site for ligands with host protein of SARS-CoV-2: (a) 2gtb-Thymoquinone, (b) 2gtb-Camphor, (c) 2gtb-Pulegone, (d) 6lu7-Thymoquinone, (e) 6lu7-Camphor, and (f) 6lu7-Pulegone.

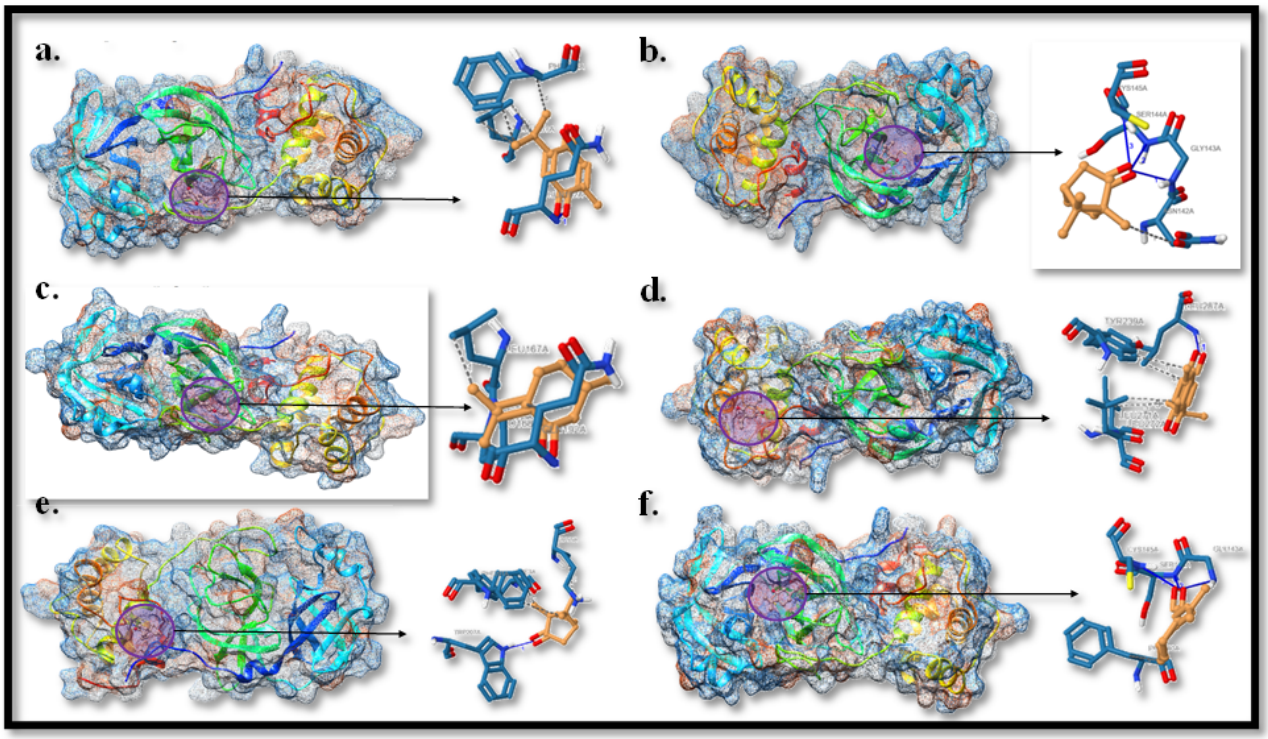


Figure 3. Binding site for ligands in protease of hosts. The active site has been highlighted, surface and cartoon representation in a black box and the cavity has been magnified to display the residues in each case. Distinct bond distance along with bond between hetero atoms and other atoms is also shown in a mess structure. Here (a) 2gtb-Thymoquinone, (b) 2gtb- Camphor, (c) 2gtb-Pulegone, (d) 6lu7-Thymoquinone, (e) 6lu7-Camphor, and (f) 6lu7-Pulegone.

CCDC Gold has been used to corroborate the Autodock results by selecting all the required parameters like torsion angle distribution, rotatable bonds, protonated ligand, flexibility, and GA setting to run the programme. It provides us the binding sites along with number of solutions as represented in **Figure 4**. The results can be analyzed by comparing the bond distances from the functional group(s) of ligands to the amino acid residue of a specific protease of the host SARS-CoV-2. For example, pulegone interacts with a lowest bond distance of 1.949 Å with THR168 amino acid residue of host 2gtb and that of camphor is 1.748 Å against host 6lu7, respectively. The host-guest bond distance also plays important role for binding interaction and it is observed that less the bond distance between the host and guest molecule more is the activity. By using Chimera tool, 3D structure of host-guest complex of best docked analogue was elucidated to determine the active binding sites of ligand with protein **(Figure 4)**.

Concepts of DFT

Initially, the geometry optimized solid state structures of the keto-based ligands are calculated through density functional theory (DFT). Also, molecular orbital energies like HOMO (E_{HOMO}) and LUMO (E_{LUMO}) were also calculated for those ligands to check their tendency to donate and/ or accept electrons towards protease hosts *viz.* 2gtb and 6lu7, respectively. The electron density in different regions of the molecule at HOMO and LUMO are generated and visualized in **Figure 5**. Furthermore, the HOMO energy (E_{HOMO}) and LUMO energy (E_{LUMO}) values of the selected natural drugs are summarized in **Table 2**. Besides, the electron density maps of molecular orbitals of the chosen keto-based ligands are shown in Figure 5, and energy or band gap (ΔE) between two molecular orbitals of the ligand is calculated with the formula: $\Delta E = E_{LUMO} - E_{HOMO}$.

The energy gap that is directly proportional to the reactivity of a molecule, can be correlated to the transition from HOMO to LUMO of a molecule [42]. As represented in **Table 2**, thymoquinone shows least band gap of ΔE = 3.82 eV between HOMO and LUMO with respect to camphor (ΔE = 5.9 eV), and pulegone (ΔE = 5.22 eV). From this band gap value, it can be concluded that thymoquinone is more stable than pulegone and camphor and should be chemically less reactive. From the docking score values, it is also observable that thymoquinone has poor binding energy value, thus, less preferable to use as antiviral drug.

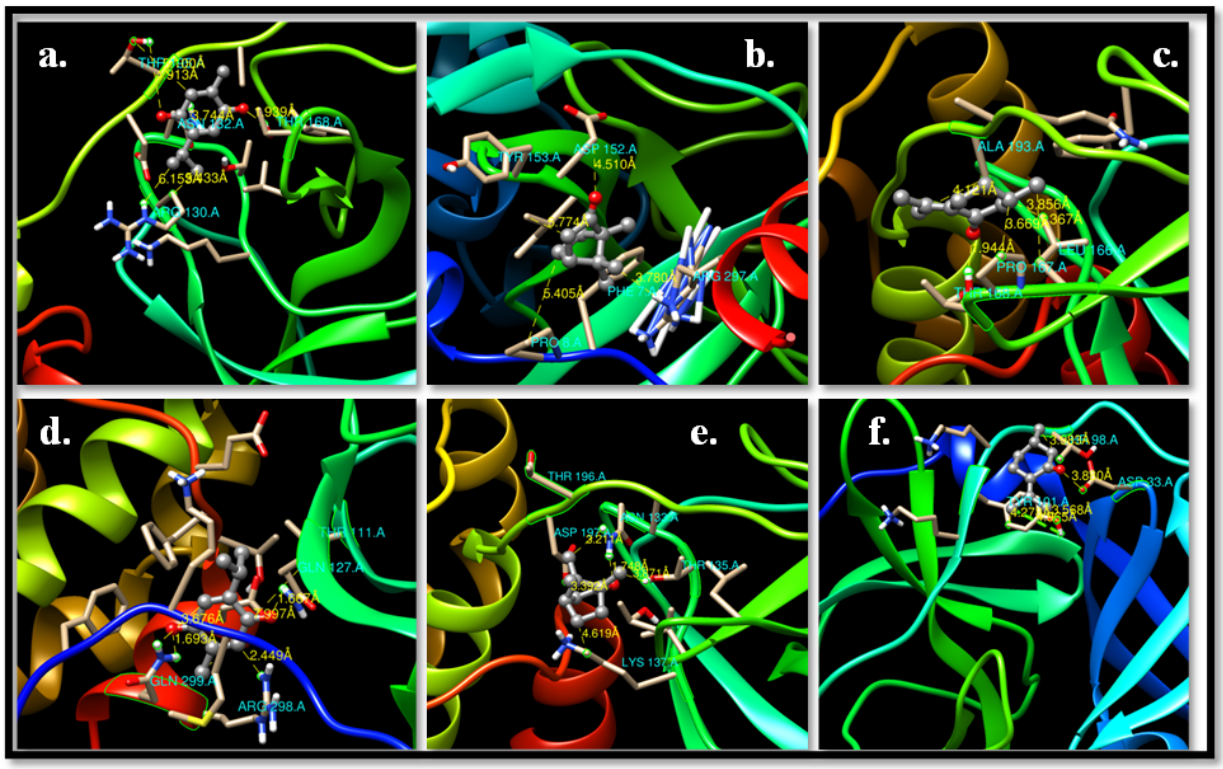


Figure 4. Binding site detection using CCDC Gold programme. Specific bond distances along with atom name and hetero atoms are displayed for each case i.e., (a) 2gtb- Thymoquinone, (b) 2gtb- Camphor, (c) 2gtb-Pulegone, (d) 6lu7-Thymoquinone, (e) 6lu7-Camphor, and (f) 6lu7-Pulegone. The smallest bond distance shows the good binding site.

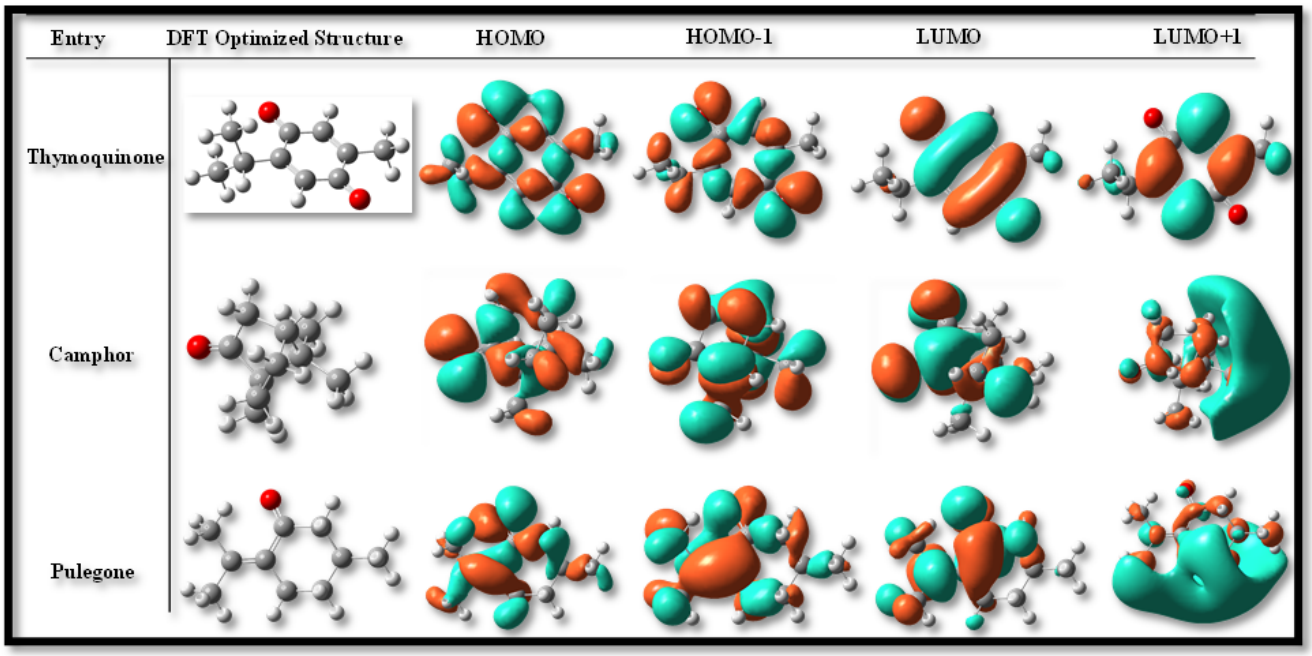


Figure 5. Electron density maps of HOMO and LUMO of keto-based ligands through DFT calculation.

Table 2. DFT calculated parameters to obtained the value of dipole moment, electro negativity (χ), absolute hardness (η) and fraction of electron transfer (ΔN).

Ligand	Total Energy (E_T in eV)	Molecular dipole Moment (Debye)	E_{HOMO} (eV)	E_{LUMO} (eV)	Band Gap (ΔE in eV)	E_{LUMO}(Fe) - E_{HOMO} (inh in eV)	Electronegativity (χ)	Absolute Hardness (η)	Fraction of electrons transfer (ΔN)
Thymoquinone	-14659.38	0.2268	-7.42	-3.60	3.82	7.29	5.51	1.91	1.03
Camphor	-12678.77	-3.3462	-6.58	-0.68	5.90	6.45	3.41	2.95	0.61
Pulegone	-12678.49	3.1750	-6.53	-1.31	5.22	6.40	3.91	2.61	0.59

Further, the ionization potential and electron affinity can be calculated by using formulas I= $-E_{HOMO}$ and A= $-E_{LUMO}$ respectively. We also derived the values of electro negativity (χ), absolute hardness (η) and fraction of electron transfer (ΔN) by using the formula $\chi = (I+A)/2$, $\eta = (I-A)/2$ and $\Delta N = \chi_{Fe}-\chi_{inh}/2(\eta_{Fe}+\eta_{inh})$, respectively. We considered the theoretical value of χ_{Fe} =0 7eV and η_{Fe} =0 eV to calculate ΔN value [16].

Again, we know that the molecular dipole moment is directly proportional to chemical reactivity [33]. Guest compounds that are taken for this study like thymoquinone, camphor, and pulegone gives molecular dipole moment of 0.2268 Debye, -3.3462 Debye, and 3.1750 Debye, respectively, which displays the best for camphor. This is exactly matching with the outcome of docking analysis as camphor shows the best activity towards host 6lu7.

CONCLUSION

Covid-19 is a viral respiratory infection caused by corona virus, which should be regulated to prevent further spread and mortality. The natural organic ligands found in various plants with potential antimicrobial or antifungal activities have been chosen for this study. Thus, these ligands can play a major role in preventing the recurrence of the virus in the gripping system and thus stopping further damage. Finding a suitable binding position inside the host protein(s) is very important to fix its viral action. Therefore, molecular docking simulation is of great interest of current research to select site specific drugs with targeted role. With the incorporation of DFT approach, this study has provided better understanding towards the chemical nature of keto-based natural drugs through defining electron density of molecules. At a glance, the outcomes of this *in silico* techniques using virtual examination can be very useful to find some phyto-compounds or natural drugs suitable for the treatment of Covid-19 viral infection.

DECLARATION OF COMPETING INTEREST

The authors declare no conflict of interest.

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