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L-amino-acids as immunity booster against COVID-19: DFT, molecular docking and MD simulations

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ABSTRACT

There is great interest to explore the importance of different amino-acids on immunity of human. Immunity helps to protect us from the pathogenic infections. The amino-acids are being use to give energy and is also used as an important basic molecule for the making of cells, protecting cell and others. Still, a little information is known for their importance in the inhibition of main protease of SARS-CoV-2. As known, tens of billions of humans are infected due to the SARS-CoV-2 and about a million of deaths are reported due to it or COVID. As of now, no promising drug is available in the market to cure the patients from this infection. Even, the medicines beings used for the partial cure may have some side effects. Therefore, the focus is to explore the natural amino-acids against the Mpro of SARS-CoV-2 as using of amino-acids is not toxic to humans. In the present work, authors have studied the amino-acids using DFT calculations and then they were explored for their promising role in the inhibition of main protease of SARS-CoV-2 using molecular docking and molecular dynamics simulations. Out of the 20 amino-acids, arginine found to best against the main protease of SARS-CoV-2 using the molecular docking and the binding energy was -0.94 kcal/ mol. Further, molecular dynamics simulations for the main protease of SARS-CoV-2 with and without arginine was performed using the Amber and different thermodynamic parameters like ΔH and $T\Delta S$ to get ΔG, comes out to be 2.74 kcal/mol. It is expected that arginine can boost the immunity.

1. Introduction

The nations across the world are suffering from the malnutrition and the infections due to various pathogens. These are the key problems of human for their survival, health and others. Therefore, the researchers have developed a new discipline related to the nutrition. The role of the nutrients in the food taken is important in the metabolism, different biological functions to provide the immunity at tissue or cell level. With decrease in the amount of protein in diet, concentration of amino-acids decreases and the drastic decrease in the immunity is observed mainly in the developing countries. Immunity acts to help in protection of human from the attack of various microbes (bacteria, fungi, virus, parasite) [1,2]. Amino-acids are being used to synthesize the new cells to fight against the microbes and to avoid infections due to microbes via inhibition. This has attracted the researchers to explore the role of amino-acids against the main protease of SARS-CoV-2 to decrease the infection from SARS-CoV-2 in patients and save their life [3–7]. Till data millions of people got infected due to this virus and the caused disease is known as COVID-19. Computational tools can be used to study the inhibition of main protease of SARS-CoV-2 using the various drugs, drug like candidates, amino-acids, Density function theory (DFT) approach is used to know about the thermodynamic parameters of the amino-acids using the Gaussian and the Gaussview (interface) [8–13]. Further, molecular docking was used to study the interaction of the small with the amino-acids present in main protease of SARS-CoV-2 and explain the interaction in the form of physical data, that is, binding energy [14–16]. Further, it can be used to screen the molecules. After then, molecular dynamics (MD) simulations was used performed to study the interaction of small molecules with the main protease of SARS-CoV-2 and the binding energy was calculated using molecular mechanics-generalized born surface analysis (MM-GBSA) [9,17,18]. Literature reported that the amino-acids can help the patients suffering from chronic congestion and sinus. Further, it can reduce the infection via targeting the replication of virus; may be helpful in cleavage of the virus etc. Even, amino-acids the units of the proteins and so produces the antibodies in human to fight against the infection

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from SARS-CoV-2 [19,20]. In the present work, authors have performed the DFT calculations of amino-acids and then their promising role in the inhibition of main protease of SARS-CoV-2 was investigated using molecular docking and molecular dynamics (MD) simulations followed MM-GBSA calculations.

2. Computational calculations

2.1. Designing of compounds

The structures of the amino-acids have been drawn using the chemdraw, a computational tool. The drawn structures were used to studied using the DFT calculations and further, they were explored for the promising ability to inhibit the main protease of SARS-CoV-2 using the molecular docking and molecular dynamics (MD) simulations [21–23].

2.2. DFT calculation

As of density-functional theory (DFT) approach is an interesting and powerful computer-based approach to know about the designed molecules for their physical and chemical properties in gaseous state as well in different state [9–11,23, 24]. It provides different thermodynamic parameters and locations of electron density on the molecule. It can also be used to get different spectroscopic spectra of the molecules. Such information can be obtained at different temperature using the DFT calculations. Authors have applied optimizations + frequency with the basis set of 6–31G* (d,p) in default on Gaussian to get the different information [25].

2.3. Molecular docking

The designed amino-acids are docked against the main protease of the new coronavirus using the Pardock, a web server developed by Gupta et al. [23]. It is a promoting tool to get information for the interaction of ligand with a receptor. It explains the interaction in the form of physical data, that is, binding energy for the formation of complex between ligand and receptor in kcal/ mol. The binding energy is obtained due to different interaction like electrostatic interactions, van der Waals interactions and hydrophobic interactions [26–32].

2.4. Molecular dynamics (MD) simulations

Molecular dynamics (MD) simulations is used to study the ligand-receptor interaction in nanoseconds to microseconds using various trajectories based on equation of motion. MD simulations was performed using the Amber18 and the molecular interaction between the ligand and receptor were performed on applying a force field, AMBER. And TIP3.0 was taken for the study. Various trajectories like root mean square deviation (RMSD), root mean square fluctuations (RMSF), hydrogen bond to can be obtained through MD simulations to know about the complex for the stability/ inhibition, fluctuation, number of hydrogen bonds. Three stages are involved in the MD production, minimizations, heating at constant temperature and volume and at constant temperature and pressure. The structure was minimized and then was equilibrated. Trajectories were obtained on every 5000 steps. A program, CPPTRAJ was used for the analysis of data obtained during MD production. RMSD is used to know the deviation of the complex in reference to the protein and if the deviation towards higher is more than considered instability. Lesser the RMSD means more the stability but it's a preliminary information. Further, RMSF used to understand the fluctuation of main protease of nCoV with and without ligand. If less fluctuation are obtained for protein in the presence of ligand, then consider to have attain more stability. More the number of hydrogen bonds means the complex may have attained more stability than the native protease. But to know about the stability and better understanding for the formation of complex, there is a need to calculate thermodynamic parameters like change in free energy. It can be done by MM-GBSA calculations [9].

Amber 18 can be used to perform the MM-GBSA calculations for the main protease of nCoV with ligand. It has a wide acceptability for the calculation of the relative change in energy for the formation of the complex. It tells about the stability of the complex or can say the feasibility for the complex at a temperature and provides reliable information. Further, the conformational entropy change ($-T\Delta S$) was determined based on the quasi-harmonic method. So, with the help of relative change in energy and the entropy, one can calculate the relative change in free energy for the formation of the complex using MM-GBSA calculations.

3. Results and discussion

3.1. DFT calculations

DFT approach was used to know the different frontier molecular orbitals like highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbitals (LUMO) to know the locations of electron density so one can tell about the nucleophilic and electrophilic site present in the molecule. All the 20 amino-acids were studied for their HOMO and LUMO at 298 K (**Fig. S1 of supporting informaation)**. One this clear after studying the HOMO and LUMO that very small electron density is located on the alkyl part of the amino-acids. Further, it is observed that the alkyl group or the functional group present on the amino-acids influence the shifting of the electron density. More of the electron density is on the amide functionality or the other functional groups present in the amino-acids [9,33–36].

Using DFT calculations, different parameters like zero-point energy, thermal energy, thermal enthalpy and free energy for the designed amino-acids have been determined to know about their stability as in **Table 1**. Based on the results obtained in the **Table 1**, zero-point energy, thermal energy, thermal enthalpy and free energy of all the amino-acids found be negative. Further, the free energy of arginine, cysteine, methionine and tryptophan found to be most negative. Further, dipole moment was calculated to study how the alkyl or the functional group influence the polarization. It is reported that more the polarization or more the dipole moment of the molecular indicates more the solubility in the water. The dipole moment of arginine found to be maximum, indicates the maximum solubility in water.

Further, different properties of the amino-acids are determined using the energies of HOMO and LUMO. One can calculate the physiochemical descriptors like chemical hardness (η), electronegativity (χ), softness (S), chemical potential (μ) and global electrophilicity index (ω) as in **Table 2**.

It is reported that higher the energy of HOMO showed ability to act as nucleophilic site and so the reactivity. Further, less the energy of LUMO showed its nature as electrophilic site and has a tendency for accepting electrons. These values help to understand the chemical hardness and the softness. Further, the energy of HOMO and LUMO gave a relationship for the polarizability. The energies of HOMO and LUMO for the amino-acids does not have significant different.

3.2. Molecular docking

The crystal structure of main protease of SARS-CoV-2 has been taken from RCSB (PDB ID: 6LU7) Molecular docking of all the amino-acids have been performed against the main protease of

Table 1
Various thermodynamic parameters Zero-point energy, thermal energy, thermal enthalpy and free energy and dipole moment for the designed amino-acids.

Name of amino-acid	Zero-point Energy (Hartree per particle)	Thermal Energy (Hartree per particle)	Thermal Enthalpy (Hartree per particle)	Thermal Free Energy (Hartree per particle)	Dipole Moment
Alanine	−321.849620	−321.843208	−321.842263	−321.879623	6.01
Arginine	−602.959381	−602.946064	−602.945120	−603.001307	8.31
Asparagine	−489.594882	−489.586131	−489.585187	−489.629006	4.13
Aspartic acid	−509.341947	−509.332920	−509.331976	−509.376360	5.20
Cysteine	−718.062008	−718.053885	−718.052941	−718.095323	6.90
Glutamic acid	−548.418336	−548.407979	−548.407035	−548.455539	5.39
Glutamine	−528.664561	−528.654522	−528.653578	−528.700405	5.92
Glycine	−282.769975	−282.764655	−282.763711	−282.799149	6.39
Histidine	−545.554774	−545.544421	−545.543476	−545.591575	5.12
Isoleucine	−439.069464	−439.059223	−439.058279	−439.105108	5.91
Leucine	−439.052066	−439.041470	−439.040525	−439.087842	3.92
Lysine	−494.080898	−494.069264	−494.068320	−494.119335	4.52
Methionine	−796.218612	−796.207654	−796.206710	−796.256797	4.80
Phenylalanine	−551.537474	−551.526300	−551.525356	−551.575535	3.75
Proline	−398.809449	−398.802375	−398.801431	−398.841316	6.23
Serine	−396.631165	−396.623892	−396.622948	−396.662754	5.49
Threonine	−435.710155	−435.701368	−435.700424	−435.743469	5.07
Tryosine	−587.255747	−587.244939	−587.243995	−587.292649	2.85
Tryptophan	−682.363462	−682.350907	−682.349963	−682.403854	7.61
Valine	−399.998307	−399.989441	−399.988497	−400.031730	5.87

Table 2
Physico-chemical descriptors of the amino-acids from the energies of HOMO and LUMO.

Name of amino-acid	E_L	E_H	E_{H-L}	E	η	X	S	μ	Ω
Alanine	0.0268	−0.234	−0.2608	−0.2072	−0.1304	0.1036	−3.8344	−0.1036	−0.0412
Arginine	0.0235	−0.1996	−0.2231	−0.1761	−0.1116	0.0881	−4.4823	−0.0881	−0.0348
Asparagine	0.0018	−0.2265	−0.2283	−0.2247	−0.1142	0.1124	−4.3802	−0.1124	−0.0553
Aspartic Acid	−0.0342	−0.2317	−0.1975	−0.2659	−0.0988	0.1330	−5.0633	−0.1330	−0.0895
Cysteine	0.0148	−0.2349	−0.2497	−0.2201	−0.1249	0.1101	−4.0048	−0.1101	−0.0485
Glutamic Acid	0.0106	−0.2453	−0.2559	−0.2347	−0.1280	0.1174	−3.9078	−0.1174	−0.0538
Glutamine	−0.0021	−0.2176	−0.2155	−0.2197	−0.1078	0.1099	−4.6404	−0.1099	−0.0560
Glycine	0.0336	−0.2314	−0.265	−0.1978	−0.1325	0.0989	−3.7736	−0.0989	−0.0369
Histidine	0.006	−0.2224	−0.2284	−0.2164	−0.1142	0.1082	−4.3782	−0.1082	−0.0513
Isoleucine	0.024	−0.2338	−0.2578	−0.2098	−0.1289	0.1049	−3.8790	−0.1049	−0.0427
Leucine	0.0047	−0.2174	−0.2221	−0.2127	−0.1111	0.1064	−4.5025	−0.1064	−0.0509
Lysine	0.0255	−0.2028	−0.2283	−0.1773	−0.1142	0.0887	−4.3802	−0.0887	−0.0344
Methionine	0.0172	−0.2174	−0.2346	−0.2002	−0.1173	0.1001	−4.2626	−0.1001	−0.0427
Phenylalanine	0.02	−0.2233	−0.2433	−0.2033	−0.1217	0.1017	−4.1102	−0.1017	−0.0425
Proline	0.0305	−0.2269	−0.2574	−0.1964	−0.1287	0.0982	−3.8850	−0.0982	−0.0375
Serine	0.0264	−0.2548	−0.2812	−0.2284	−0.1406	0.1142	−3.5562	−0.1142	−0.0464
Threonine	0.0181	−0.2429	−0.261	−0.2248	−0.1305	0.1124	−3.8314	−0.1124	−0.0484
Tryptophan	−0.0212	−0.213	−0.1918	−0.2342	−0.0959	0.1171	−5.2138	−0.1171	−0.0715
Tyrosine	−0.0078	−0.221	−0.2132	−0.2288	−0.1066	0.1144	−4.6904	−0.1144	−0.0614
Valine	0.0234	−0.2345	−0.2579	−0.2111	−0.1290	0.1056	−3.8775	−0.1056	−0.0432

Table 3
Binding energy obtained using molecular docking against the main protease of SARS-CoV-2.

Name of amino-acid	Binding energy (kcal/mol)	Name of amino-acid	Binding energy (kcal/mol)
Alanine	−0.94	Leucine	−1.87
Arginine	−2.92	Lysine	−1.76
Asparagine	−0.56	Methionine	−2.70
Aspartic Acid	−2.16	Phenylalanine	−2.74
Cysteine	−2.66	Proline	−0.95
Glutamic Acid	−1.40	Serine	−0.80
Glutamine	−1.29	Threonine	−1.79
Glycine	−0.54	Tryptophan	−2.34
Histidine	−2.20	Tyrosine	−2.28
Isoleucine	−1.23	Valine	−0.93

SARS-CoV-2 using Pardock and the data is given in **Table 3**. Based on the results obtained, arginine found to be most promising inhibition ability against the main protease of SARS-CoV-2 as the binding energy found to be −2.92 kcal/mol. Two- and three-dimensional view for the interaction of arginine with the amino-acids of the main protease of SARS-CoV-2 are given **Fig. 1**. Herein, the arginine interacts with PRO, GLN and GLU of the main protease of SARS-CoV-2.

3.3. Molecular dynamics simulations

For a better understanding of the interaction of main protease of SARS-CoV-2 with and without arginine using molecular dynamics (MD) simulations. Trajectories of RMSD and RMSD are determined as in **Fig. 2** and **Fig. 3**, respectively.

Based on **Fig. 2**, the RMSD values of complex (main protease of SARS-CoV-2 -Arginine) is higher than the for the main protease of

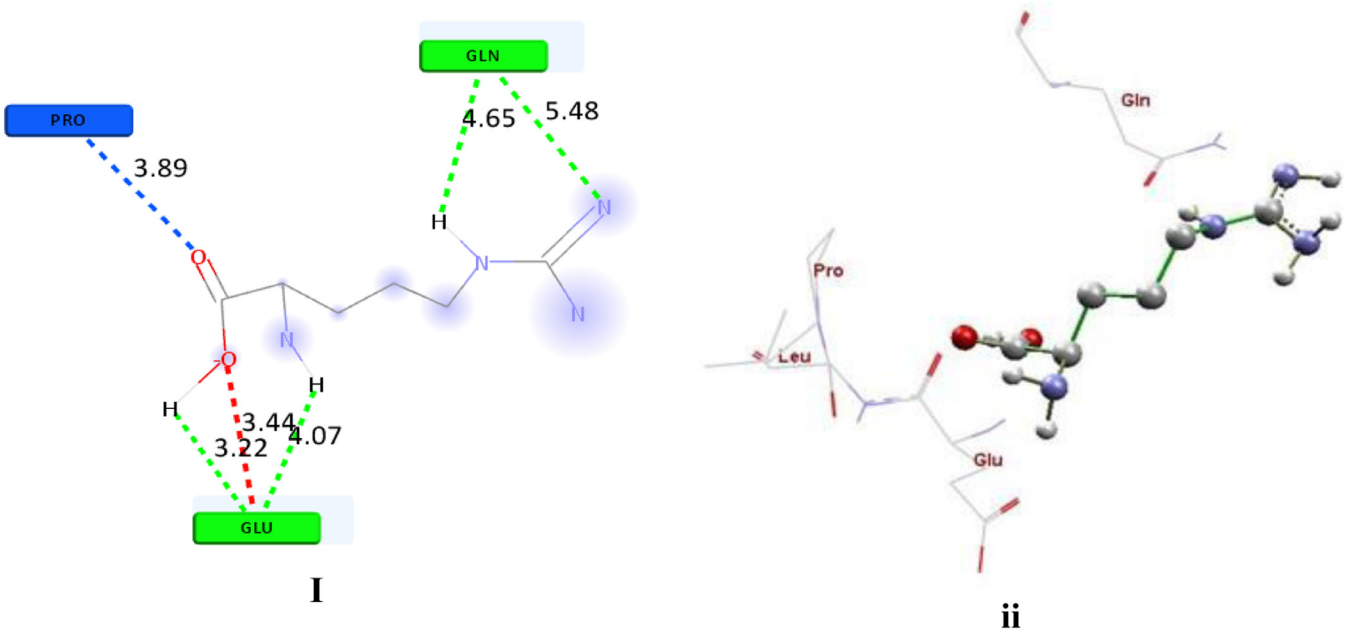

Fig. 1. (i) Two and (ii) three dimensional views for the interaction of arginine with amino-acids of the main protease of SARS-CoV-2.

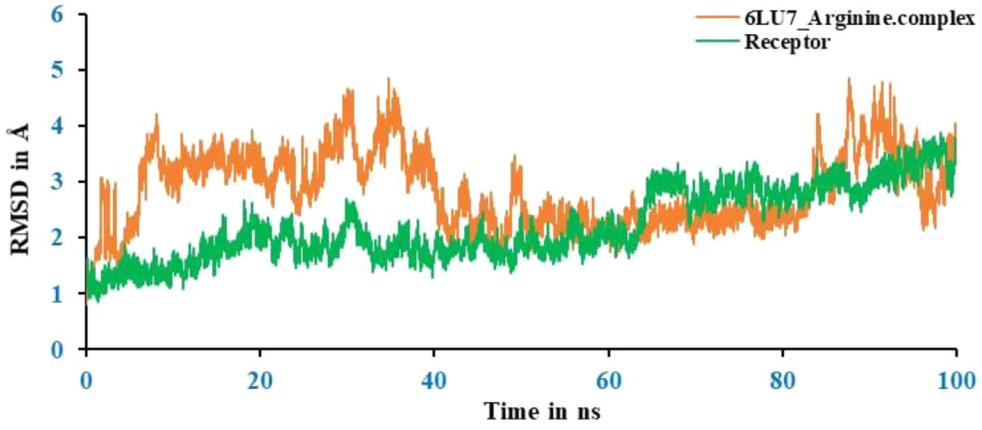

Fig. 2. RMSD plot of main protease of SARS-CoV-2 with and without arginine.

Table 4
Calculation to determine the change in Entropy for the formation of complex between main protease of SARS-CoV-2 and arginine.

Systems	Translational	Rotational	Vibrational	Total
Complex	17.0101	17.7682	4926.2654	4961.0440
Receptor	17.0056	17.7662	4863.9630	4898.7348
Ligand	12.3270	9.1079	48.6238	70.0590
TΔS	−12.3225	−9.1058	13.6785	−7.7498

SARS-CoV-2 alone in beginning. But on increasing time, the RMSD values of the complex is decreasing and RMSD values for the main protease of SARS-CoV-2 decreases.

Based on Fig. 3, the fluctuation for the complex is less than for the main protease of SARS-CoV-2. So, it can be concluded that the stability increases on complexation.

3.4. Calculation to determine the change in entropy

Using MM-GBSA calculations, relative change in entropy for the complex, ligand (arginine) and the receptor (main protease of SARS-CoV-2) was calculated as in Table 4 to determine relative change in entropy for the formation of complex**,** as an important input to get relative change in free energy for the formation of complex. The relative change of entropy for the formation of complex is −7.7498 kcal/mol.

3.5. Relative change in enthalpy for the formation of the complex

Another parameter to calculate change in free energy for the formation of complex is relative change in enthalpy (Tabke 5). MM-GBSA calculations for the complex for a simulation time of 100 ns gave the relative change in enthalpy and can be understood from the Fig. 4.

The relative change in enthalpy is obtained by the contribution of various factor as shown in the Fig. 5 and Table 4. These are energy contribution by different interactions (van der Waals, electrostatic etc.) and free energy (gaseous and solvent). It comes out to −5.0 kcal/mol.

Therefore, the change in free energy for the formation of complex (ΔG) comes out to be = 2.74 kcal/mol.

There is a need to understand the vaccine made up of viral antigenic fragments and they are obtained from different techniques. They can be easily produced, safer than many as well as more tol-

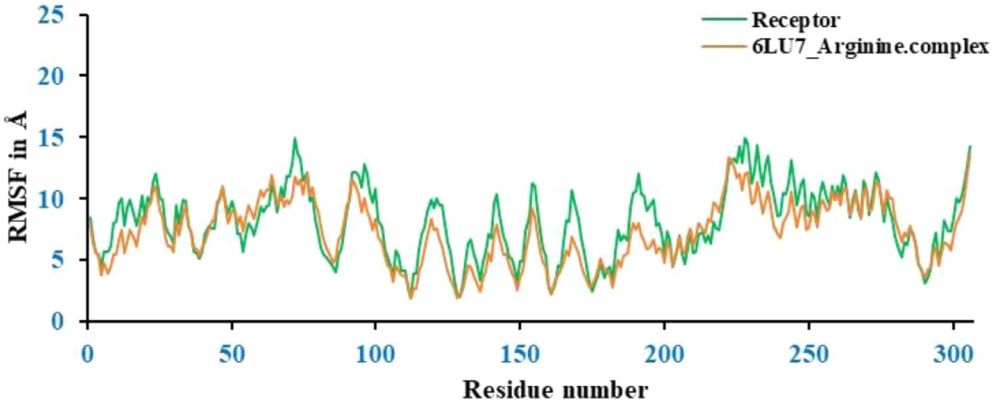

Fig. 3. RMSF plot of main protease of SARS-CoV-2 with and without arginine.

Table 5
Determine the change in enthalpy for the formation of complex between main protease of SARS-CoV-2 and arginine.

Energy component	6LU7_Arginine. complex Average	Receptor Average	Ligand Average	6LU7_Arginine.complex - Receptor - Ligand (kcal/mol) Average
E_{vdW}	−2380.52	−2371.74	−1.19	−7.58
E_{EL}	−21,397.82	−21,402.71	17.44	−12.55
E_{GB}	−3097.40	−3080.19	−33.55	16.34
E_{SURF}	109.32	108.54	1.99	−1.21
ΔG_{Gas}	−23,778.34	−23,774.45	16.24	−20.13
ΔG_{Solv}	−2988.07	−2971.65	−31.55	15.13
ΔH	−26,766.42	−26,746.11	−15.30	−5.00

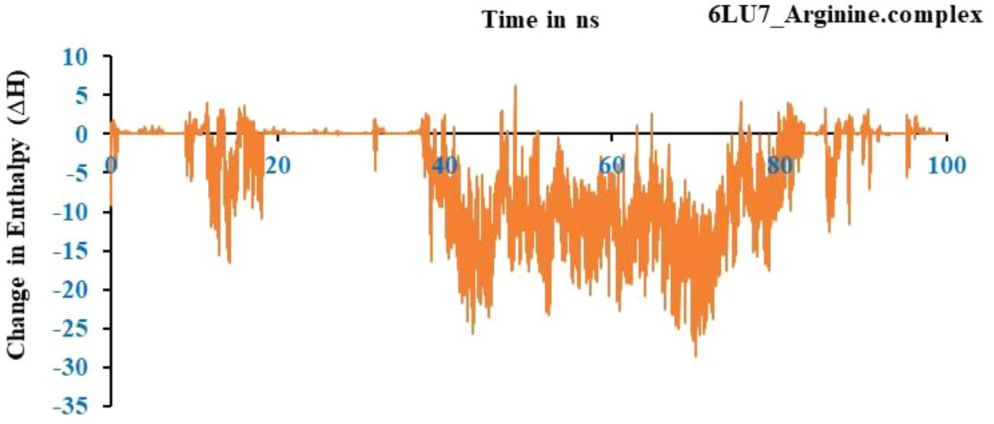

Fig. 4. Relative change in enthalpy for the formation of complex between main protease of SARS-CoV-2 and arginine.

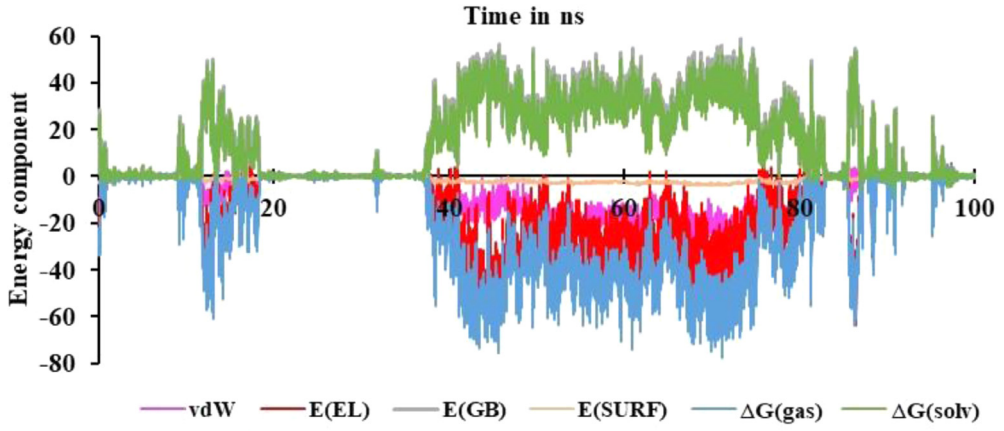

Fig. 5. Various relative change in energy for the formation of complex between main protease of SARS-CoV-2 and arginine.

erated than other vaccines based on whole virus or the vector. There is an issue with vaccine having protein, that is, poor immunogenicity of the vaccine. Further, there may be need of booster to increase the potential of such vaccines. Therefore, immunostimulatory molecules are used with protein subunit to get the vaccine or come out from this limitation. Initially, vaccines were based on whole or complete S-protein but later on, researchers are working on the S-protein RBD bases vaccines. At present, no protein-based vaccine is under clinical trial. There is also an issue of the production of such vaccine at large scale. In the present work based on molecular dynamics simulations, we reach to the conclusion that arginine may inhibit the Mpro of nCoV effectively. We have mentioned that it can be an immunity booster so the possibility of infection due to nCoV will be less [19,37].

4. Conclusion

Amino-acids can help the patients suffering from chronic congestion and sinus. Further, it can reduce the infection via targeting the replication of virus; may be helpful in cleavage of the virus etc. Even, amino-acids are the units of the proteins and so produces the antibodies in human to fight against the infection from SARS-CoV-2. In the present work, twenty amino-acids are explored for their chemical properties using DFT approach. Further, the amino-acids were targeted against the main protease of SARS-CoV-2 and arginine have shown the best binding and it is −0.94 kcal/ mol. Molecular dynamics simulations for the main protease of SARS-CoV-2 with and without arginine was performed using the Amber to get the thermodynamic parameters like change in enthalpy (ΔH) and relative change in entropy (ΔS) to get change in free energy (ΔG) for the formation of complex and it is 2.74 kcal/mol.

Disclosure of potential conflicts of interest

We, the corresponding authors declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. IWe further confirm that the order of authors listed in the manuscript has been approved by all of us.

Research involving human participants and/or animals

It is declared that no human participants and/or animals are used in this work.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2021.131924.

References

[1] A.D. Elmezayen, A. Al-Obaidi, A.T. Şahin, K. Yelekçi, Drug repurposing for coronavirus (COVID-19): *in silico* screening of known drugs against coronavirus 3CL hydrolase and protease enzymes, J. Biomol. Struct. Dyn. (2020), doi:10.1080/07391102.2020.1758791.

[2] R.Z. Hamza, T. Al-Talhi, A.A. Gobouri, W.F. Alsanie, S.M. El-Megharbel, Are favipiravir and acyclovir with IgG injections supplemented with vitamin D "suggested therapeutic option" can fight against COVID-19? Adv. Anim. Vet. Sci. 9 (2021), doi:10.17582/journal.aavs/2021/9.4.549.554.

[3] C.N. Patel, D. Goswami, D.G. Jaiswal, R.M. Parmar, H.A. Solanki, H.A. Pandya, Pinpointing the potential hits for hindering interaction of SARS-CoV-2 S-protein with ACE2 from the pool of antiviral phytochemicals utilizing molecular docking and molecular dynamics (MD) simulations, J. Mol. Graph. Model. 105 (2021), doi:10.1016/j.jmgm.2021.107874.

[4] K.M. White, R. Rosales, S. Yildiz, T. Kehrer, L. Miorin, E. Moreno, S. Jangra, M.B. Uccellini, R. Rathnasinghe, L. Coughlan, C. Martinez-Romero, J. Batra, A. Rojc, M. Bouhaddou, J.M. Fabius, K. Obernier, M. Dejosez, M.J. Guillén, A. Losada, P. Avilés, M. Schotsaert, T. Zwaka, M. Vignuzzi, K.M. Shokat, N.J. Krogan, A. García-Sastre, Plitidepsin has potent preclinical efficacy against SARS-CoV-2 by targeting the host protein eEF1A, Science 371 (2021) (80-.), doi:10.1126/science.abf4058.

[5] A. Kumar, V. Kumar, K. Kumari, P. Jain, N.K. Kaushik, P. Singh, Promising iron(II) complexes of curcumins: designing, density functional theory, and molecular docking, J. Phys. Org. Chem. 34 (2021), doi:10.1002/poc.4196.

[6] M.K. Tripathi, P. Singh, S. Sharma, T.P. Singh, A.S. Ethayathulla, P. Kaur, Identification of bioactive molecule from Withania somnifera (Ashwagandha) as SARS-CoV-2 main protease inhibitor, J. Biomol. Struct. Dyn. (2020), doi:10.1080/07391102.2020.1790425.

[7] S. Ghandehari, Progesterone for the Treatment of COVID-19 in Hospitalized Men, ClinicalTrials.Gov, 2020.

[8] . https://en.wikipedia.org/wiki/Gaussian_(software).

[9] D. Kumar, M.K. Meena, K. Kumari, R. Patel, A. Jayaraj, P. Singh, In-silico prediction of novel drug-target complex of nsp3 of CHIKV through molecular dynamic simulation, Heliyon 6 (2020), doi:10.1016/j.heliyon.2020.e04720.

[10] A. Kumar, K. Kumari, S. Singh, I. Bahdur, P. Singh, Noscapine anticancer drug designed with ionic liquids to enhance solubility: DFT and ADME approach, J. Mol. Liq. 325 (2021), doi:10.1016/j.molliq.2020.115159.

[11] M.Y. Cui, J.X. Nie, Z.Z. Yan, M.W. Xiao, D. Lin, J. Ye, A.X. Hu, Design, synthesis, bioactivity, and DFT calculation of 2-thiazolyl-hydrazone derivatives as influenza neuraminidase inhibitors, Med. Chem. Res. 28 (2019), doi:10.1007/s00044-019-02343-3.

[12] O.E. Sherif, N.S. Abdel-Kader, DFT calculations, spectroscopic studies, thermal analysis and biological activity of supramolecular Schiff base complexes, Arab. J. Chem. 11 (2018), doi:10.1016/j.arabjc.2015.07.008.

[13] M. Hagar, H.A. Ahmed, G. Aljohani, O.A. Alhaddad, Investigation of some antiviral N-heterocycles as COVID 19 drug: molecular docking and DFT calculations, Int. J. Mol. Sci. 21 (2020), doi:10.3390/ijms21113922.

[14] A. Frediansyah, F. Nainu, K. Dhama, M. Mudatsir, H. Harapan, Remdesivir and its antiviral activity against COVID-19: a systematic review, Clin. Epidemiol. Glob. Health 9 (2021), doi:10.1016/j.cegh.2020.07.011.

[15] D. Kumar, K. Kumari, A. Jayaraj, V. Kumar, R.V. Kumar, S.K. Dass, R. Chandra, P. Singh, Understanding the binding affinity of noscapines with protease of SARS-CoV-2 for COVID-19 using MD simulations at different temperatures, J. Biomol. Struct. Dyn. 39 (2021), doi:10.1080/07391102.2020.1752310.

[16] K. Kumari, A. Kumar, I. Bahadur, P. Singh, Investigate the interaction of testosterone/progesterone with ionic liquids on varying the anion to combat COVID-19: density functional theory calculations and molecular docking approach, J. Phys. Org. Chem. (2021), doi:10.1002/poc.4273.

[17] V.K. Vishvakarma, N. Shukla, K. Kumari, R. Patel, P. Singh, Reetu, A model to study the inhibition of nsP2B-nsP3 protease of dengue virus with imidazole, oxazole, triazole thiadiazole, and thiazolidine based scaffolds, Heliyon 5 (2019), doi:10.1016/j.heliyon.2019.e02124.

[18] D. Kumar, P. Singh, A. Jayaraj, V. Kumar, K. Kumari, R. Patel, A Theoretical model to study the interaction of erythro-noscapines with nsP3 protease of Chikungunya virus, ChemistrySelect. 4 (2019), doi:10.1002/slct.201803360.

[19] D. Tomé, Amino acid metabolism and signalling pathways: potential targets in the control of infection and immunity, Eur. J. Clin. Nutr. 75 (2021), doi:10.1038/s41430-021-00943-0.

[20] K. Fukumoto, M. Yoshizawa, H. Ohno, Room temperature ionic liquids from 20 natural amino acids, J. Am. Chem. Soc. 127 (2005) 2398–2399, doi:10.1021/ja043451i.

[21] T. Brown, ChemDraw, Sci. Teach. 81 (2014).

[22] M.J. Frisch, G.W. Trucks, H.E. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, G.A. Petersson, F. O, J.B. Foresman, J.D. Fox, Gaussian 16, Gaussian, Inc., Wallingford CT, 2016.

[23] A. Gupta, P. Sharma, B. Jayaram, ParDOCK: an all atom energy based Monte Carlo docking protocol for protein-ligand complexes, Protein Pept. Lett. 14 (2007), doi:10.2174/092986607781483831.

[24] A. Singh, S. Singh, S. Sewariya, N. Singh, P. Singh, A. Kumar, R. Bandichhor, R. Chandra, Stereospecific N-acylation of indoles and corresponding microwave mediated synthesis of pyrazinoindoles using hexafluoroisopropanol, Tetrahedron 84 (2021), doi:10.1016/j.tet.2021.132017.

[25] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, G.A. Petersson, H. Nakatsuji, Gaussian 16, 2016, {Gaussian}, Inc., Wallingford CT, 2016.

[26] N. Baildya, N.N. Ghosh, A.P. Chattopadhyay, Inhibitory activity of hydroxychloroquine on COVID-19 main protease: an insight from MD-simulation studies, J. Mol. Struct. 1219 (2020), doi:10.1016/j.molstruc.2020.128595.

[27] M. Kumari, U.K. Singh, P. Singh, R. Patel, Effect of N-Butyl-N-Methyl-Morpholinium bromide ionic liquid on the conformation stability of human serum albumin, ChemistrySelect 2 (2017), doi:10.1002/slct.201601477.

[28] K.C. Hsu, Y.F. Chen, S.R. Lin, J.M. Yang, Igemdock: a graphical environment of enhancing gemdock using pharmacological interactions and post-screening analysis, BMC Bioinform. 12 (2011), doi:10.1186/1471-2105-12-S1-S33.
[29] A. Kumar, D. Kumar, R. Kumar, P. Singh, R. Chandra, K. Kumari, DFT and docking studies of designed conjugates of noscapines & repurposing drugs: promising inhibitors of main protease of SARS-CoV-2 and falcipan-2, J. Biomol. Struct. Dyn. (2020), doi:10.1080/07391102.2020.1841030.
[30] V.K. Vishvakarma, P. Singh, K. Kumari, R. Chandra, Rational design of threo as well erythro noscapines, an anticancer drug: a molecular docking and molecular dynamic approach, Biochem. Pharmacol. Open Access 06 (2017), doi:10.4172/2167-0501.1000229.
[31] R.R. Maurya, V. Mohan, P. Singh, S. Singh, I. Bahadur, A novel benzimidazole based cadmium (II) dinuclear complex as bioactive material with different coordination number and their interactions with BSA and HSA: synthesis, characterization and docking studies, J. Mol. Liq. 328 (2021), doi:10.1016/j.molliq.2021.115471.
[32] D. Mishra, R.R. Maurya, K. Kumar, N.S. Munjal, V. Bahadur, S. Sharma, P. Singh, I. Bahadur, Structurally modified compounds of hydroxychloroquine, remdesivir and tetrahydrocannabinol against main protease of SARS-CoV-2, a possible hope for COVID-19: docking and molecular dynamics simulation studies, J. Mol. Liq. 335 (2021), doi:10.1016/j.molliq.2021.116185.
[33] D.A. Case, R.C. Walker, T.E. Cheatham, C. Simmerling, A. Roitberg, K.M. Merz, R. Luo, T. Darden, Amber 18, 2018, University of California, San Francisco, 2018.
[34] E. Wang, H. Sun, J. Wang, Z. Wang, H. Liu, J.Z.H. Zhang, T. Hou, End-point binding free energy calculation with MM/PBSA and MM/GBSA: strategies and applications in drug design, Chem. Rev. 119 (2019), doi:10.1021/acs.chemrev.9b00055.
[35] M.K. Meena, D. Kumar, A. Jayaraj, A. Kumar, K. Kumari, L.M. Katata-Seru, I. Bahadur, V. Kumar, A. Sherawat, P. Singh, Designed thiazolidines: an arsenal for the inhibition of nsP3 of CHIKV using molecular docking and MD simulations, J. Biomol. Struct. Dyn. (2020), doi:10.1080/07391102.2020.1832918.
[36] S. Sharma, S. Deep, *In-silico* drug repurposing for targeting SARS-CoV-2 main protease (Mpro), J. Biomol. Struct. Dyn. (2020), doi:10.1080/07391102.2020.1844058.
[37] Y. Der Li, W.Y. Chi, J.H. Su, L. Ferrall, C.F. Hung, T.C. Wu, Coronavirus vaccine development: from SARS and MERS to COVID-19, J. Biomed. Sci. 27 (2020), doi:10.1186/s12929-020-00695-2.