Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Journal of Molecular Structure 1251 (2022) 131965

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: www.elsevier.com/locate/molstr

Interactions between main protease of SARS-CoV-2 and testosterone or progesterone using computational approach

Vijay Kumar Vishvakarma[a], Shweta Pal[a], Prashant Singh[a,*], Indra Bahadur[b,*]

[a] Department of Chemistry, Atma Ram Sanatan Dharma College, University of Delhi, New Delhi, India
[b] Chemistry Department, Faculty of Natural and Agricultural Sciences, North-West University, Mmabatho 2735, South Africa

ARTICLE INFO

Article history:
Received 28 July 2021
Revised 13 November 2021
Accepted 17 November 2021
Available online 20 November 2021

Keywords:
Progesterone
Testosterone
Main protease of SARS-CoV-2
Molecular docking
Molecular Dynamics Simulations

ABSTRACT

SARS-CoV-2 is drastically spread across the globe in a short period of time and affects the lives of billions. There is a need to find the promising drugs like candidates against the inhibition of novel corona virus or SARS-CoV-2. Herein, the interaction on sex hormones (testosterone and progesterone) with Mpro of SARS-CoV-2 was investigated with the help of molecular docking. The binding energy for the formation complex between the progesterone and testosterone with main protease of SARS-CoV-2 are -86.05 and -91.84 kcal/mol, respectively. From this, it can be understood that testosterone showed better binding affinity with Mpro of nCoV and thus, more inhibition of the main protease. Then, the binding was further studied using molecular dynamics simulations at different temperatures (300, 310 and 325) K. It has been observed that the formations of complex between the Mpro of nCoV with testosterone/ progesterone is better at 300 K than 310 and 325 K. Further, it is found that the more effective binding of testosterone with Mpro of nCoV is observed than the progesterone based on the RMSD, RMSF and H-bond trajectories. Results indicate the promising nature of testosterone towards the inhibition of Mpro of nCoV.

© 2021 Elsevier B.V. All rights reserved.

1. Introduction

Novel Corona virus disease (COVID-19) was first reported in Wuhan in 2019 and after then, cases were reported from all the nations across the globe in a short period of time and affects the lives and economic outcomes of whole world. [1–5] Common symptoms of new corona virus infections are fever, headache, chills, dry coughing, and breathlessness. SARS-CoV-2 has infected billions of people resulted about millions of deaths worldwide. Many people are found to be asymptomatic and recovered without medical intervention but those peoples are already suffering from any kind of illness, diabetes, asthma and respiratory disorders need medical treatments [4,6–9]. Remdesivir is a nucleotide prodrug that helps to inhibit viral- RNA dependent RNA-polymerases, that plays an important role in replication of viruses including coronaviridae. [10,11] Peoples suffering from COVID-19 are treated with remdesivir and other repurposing drugs while those suffering with hypoxia, require oxygen support. It is expected that the hormones, progesterone and testosterone might interact with nCoV. [12–15] **Progesterone** causes the endometrium transition from proliferative phase to the secretory phase for maintain the blastocyst and maintain the pregnancy. It also plays an important role for maintaining the several types of tissues that are not belonged to the reproductive systems like mammary glands for breastfeeding, cardiovascular system bones. It's a steroid based hormone and known as preg-4-ene-3, 20–dione. It can be used in the medications by the combination of estrogen to five the hormonal therapies to the for menopausal systems and low hormonal women [1,14,16–21]. **Testosterone** is found in males and formed in testicles in the leydig cells while in the female ovaries also make testosterone in small amounts. It plays major role in the production of sperms in the male, secondary sexual characteristics and effects the development of body mass, bones and red blood cell production. This belongs to the class having the keto and hydroxyl at 13 and 17 positions, respectively. It shows action when on binding with the androgen receptors, or by conversion of estradiol to activate the androgen receptors [16,18,22–24]. Progesterone decreases the innate immune response while increases the immune tolerance and antibody production that leads to the increase immune dysregulation that causes COVID-19 cytokine storm. The combination is the viable options for the therapeutic treatment of the COVID-19 patients. It has been seen that the females are less effected and severe condition as compared to the males [15,25–28]. Further, low levels of testosterone in the male shows the ills effect in the endothelial cell functioning, that show low immune responses that

* Corresponding authors.
E-mail addresses: psingh@arsd.du.ac.in (P. Singh), bahadur.indra@nwu.ac.za (I. Bahadur).

https://doi.org/10.1016/j.molstruc.2021.131965
0022-2860/© 2021 Elsevier B.V. All rights reserved.

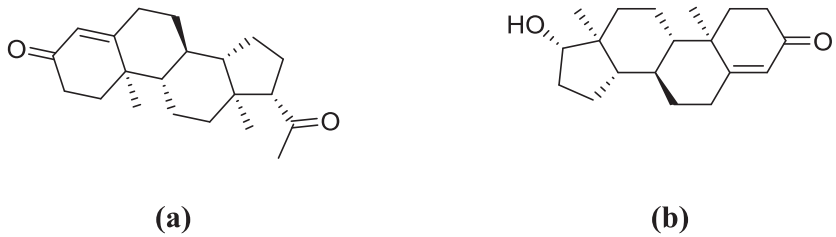

Fig. 1. Structure of (a) progesterone and (b) testosterone.

effects the ability to fight with SARS-CoV-2 and causes the inflammation. Decreased level of serum testosterone has poor effect on the COVID-19 patients by deregulating the pulmonary protective pathways [16]. Molecular dynamics (MD) stimulations is used to investigate the atom's site in the space. In this approach, the dynamic model is under the force of motion that can be studied. This motion of the stimulations can be studies by different numerical of solution like classical Newtonian dynamic equations that gives the information about the atoms sites in the molecule along with thermodynamic properties of the molecules. [29–33] In the present work, authors have investigated the interaction of testosterone and progesterone against Mpro of nCoV using molecular docking and temperature dependent molecular dynamics simulations (300, 310 and 325 K).

2. Theoretical calculations

2.1. Designing of the ligands

The structure of hormones (progesterone and testosterone) are drawn using chemdraw as mentioned in Fig. 1. These two structures were optimized before performing molecular docking and molecular dynamics simulations. The crystal structure of Mpro of nCoV (PDB ID- 6LU7) in complex with an inhibitor N3 was taken from the RCSB (10.2210/pdb6LU7/pdb) and the same prepared before the molecular docking and molecular dynamics simulations using Chimera. Further, the change in the structure of main protease of the SARS-CoV-2 in presence of progesterone and testosterone were investigated using the molecular dynamics (MD) simulations at 300 K, 310K and 325 K [7,34–39].

2.2. Molecular docking

Molecular docking of progesterone (Pr) and testosterone (T) with Mpro of nCoV was performed using iGemDock [40] and gives the binding energy for the formation of the complex using different various dockings option available [41]. The binding obtained is the combination of energy due hydrogen bonding, electrostatic and van der Waals interactions. The parameters like population size, generations and number of solutions selected for performing docking with accuracy. Very slow docking was performed to get 10 solutions of each docking and considered to be most reliable than others (standard, stable, rough and custom). This approach has been applied in this work and got 10 solutions for each compound as in Table 1.

2.3. Molecular dynamics (MD) simulations

Molecular dynamics simulations of Mpro of nCoV in presence of Pr and T were performed using the online WEBGRO Macromolecular Simulations server (https://simlab.uams.edu/ProteinWithLigand/protein_with_ligand.html). It is important to mention that it is a GRACE High Performance Computing Facility and made available by the University of Arkansas for Medical Sciences (UAMS) as a public service and the same was developed by M. Balasubramaniam, & P. Williams. Before performing MD simulations, the topology of the ligands was created using the Prodrug, that is, GlycoBioChemPRODRG2 server. (http://davapc1.bioch.dundee.ac.uk/cgi-bin/prodrg) The force filed applied to perform the MD simulations is GORMACS43a1; further, SPS water model in triclinic system and sodium chloride were taken. Then, the energy of the protein-ligand complex was minimized using the steepest descent integrator at every 5000 steps. The equilibration NVT/ NPT was performed first at 300 K and 1 bar pressure. Then, the MD integrator was Leap-frog for 100 ns and the frames per MD simulations fixed to 1000. MD simulations gave various trajectories like the root mean square deviation (RMSD), root mean square fluctuation (RMSF), radius of gyration (Rg), solvent accessible surface area (SASA), and hydrogen bonds (HBs). With the help of these trajectories, one can discuss the inhibition of Mpro of nCoV using Pr and T at 300, 310 and 325 K. [42–45].

3. Results and discussion

3.1. Molecular docking

Ten solutions for the docking between the progesterone (Pr)/ testosterone (T) with MPro of nCoV are obtained and the best pose has been taken for the investigation. The binding energy for the formation complex between the progesterone and testosterone with Mpro of nCoV are −86.05 and −91.84 kcal/mol respectively. From Table 1, it can be understood that testosterone showed better binding with Mpro of nCoV and thus, expecting more inhibition. The results obtained from molecular docking are generally not reliable, therefore, there is a need to understand the binding through different approaches like molecular dynamics simulations for sufficient.

Further, the interaction between amino-acids of Mpro of nCoV and progesterone/ testosterone after molecular docking can be investigated from docked views (Fig. 2) and the data available in Table 2. It is found that progesterone forms hydrogen bond with the THR26 (classical) as well as with MET165 (non-classical) and THR25 (non-classical). Progesterone forms hydrophobic interaction with CYS145. Further the interactions of testosterone with Mpro of nCoV was investigated. It was found that testosterone forms hydrogen bond with the SER144 (classical), LEU141 (classical), GLY143 (classical) and CYS145 (classical) as well as with ARG188 (non-classical) and ASN142 (non-classical). It also forms hydrophobic interaction with HIS41, HIS163 and CYS145.

3.2. Molecular dynamics (MD) simulations

MD simulations is an advance technique to analyze the configurational changes that occur after the induced fitting of ligand. The system is evolved using classical mechanics for few nanoseconds (ns). MD generates trajectories and the points of trajectories were used for the further analysis. These following parameters {radius of gyration (Rg), root mean square deviation (RMSD), root mean square fluctuation (RMSF), and number of hydrogen bonds}

Table 1
Binding energy obtained using molecular docking for the formation of the complex between the Mpro of nCoV in presence of progesterone or testosterone individually.

Compounds	$E_{Binding\ energy}$ (kcal/mol)	E_{VDW} (kcal/mol)	$E_{Hbonding}$ (kcal/mol)
Progesterone-0	−85.8716	−78.3564	−7.51513
Progesterone-1	−66.5682	−55.41	−11.1581
Progesterone-2	−86.0145	−79.0145	−7
Progesterone-3	−84.7612	−75.4354	−9.32584
Progesterone-4	−84.7874	−75.4392	−9.34816
Progesterone-5	−84.7809	−75.5145	−9.26636
Progesterone-6	−84.7611	−75.4339	−9.3272
Progesterone-7	−84.0137	−82.8708	−1.14298
Progesterone-8	−84.7041	−75.3562	−9.34794
Progesterone-9	−86.0568	−78.2143	−7.8426
Testosterone-0	−78.3785	−63.64	−14.7386
Testosterone-1	−87.5437	−75.4036	−12.1401
Testosterone-2	−78.4694	−70.3577	−8.11175
Testosterone-3	−78.6394	−64.1202	−14.5192
Testosterone-4	−91.8406	−72.5204	−19.3202
Testosterone-5	−77.1043	−65.1371	−11.9673
Testosterone-6	−77.5379	−66.1792	−11.3588
Testosterone-7	−71.6886	−58.9562	−12.7324
Testosterone-8	−91.635	−74.5474	−17.0877
Testosterone-9	−74.6947	−63.3001	−11.3945

Table 2
Interaction between amino-acids of Mpro of nCoV and progesterone/ testosterone after molecular docking.

Compound	H-Bond					
	Classical		Non-classical		Hydrophobic	
	Amino Acid	Distance (Å)	Amino Acid	Distance (Å)	Amino Acid	Distance (Å)
Progesterone	THR26	2.11	MET165	2.80	CYS145	4.33
			THR25	2.26		
Testosterone	SER144	3.12, 182	ARG188	2.17	HIS41	5.46
	LEU141	2.44	ASN142	2.99	HIS163	5.09
	GLY143	2.62			CYS145	4.44
	CYS145	2.55				

were calculated. Further, these parameters were used to analyze the configurational stability of the protein-ligand complex. Herein, protein-ligand complex was subjected to simulate for 100 ns to analyze the configuration changes that occur within. Initially, protein-ligand system was subjected to neutralize by applying FORCE-FIELD Gormacs and adding Na+ ion for positive deficiencies and Cl^- ion for negative deficiencies. Then, the system is solvated by adding water and optimized to the minimum energy values. Further, ensemble hypothesis was used to grow the system. Constant temperature (NVT) and pressure (NPT) were applied. In Last system was allowed to run MD simulations for 100 ns and trajectories were recorded at appropriate time. SPC waters, Na and Cl were added to the simulation box for testosterone /progesterone are 15,141/17,798, 50/57 and 46/53 respectively.

Radius of gyration (Rg) is the distance to define strength of system to bear strain. It is measured by measuring the distance between rotational axis and center of mass. For the protein-ligand system, it can be used to describe the conformational stability. Less the value of Rg indicates more conformational stability. It means that the center of mass of protein is closer to the axis of rotation. However, invariant value of Rg shows the stability due to whole time span of simulation. Herein, Rg values for Mpro of nCoV with testosterone and progesterone were studied for 100 ns at 300, 310 and 325 K. The Rg values for the complexes range between 2.14–2.18 nm and showed enough conformational stability. However, the variation in the Rg value is much considerable during complete time span of simulations. At 300 K, the variation in Rg value is less and shows stability of complex during the course of simulation and this more inhibition. After increasing temperature from 300 K to 310 K and 325 K, the behavior of Rg values changes. It was found that Rg value decreases however, more decreases were reported at 310 K. This decrease in Rg value shows the lowest value for Mpro of nCoV in case of progesterone on comparison with testosterone. Most effective inhibition of Mpro of nCoV was estimated at 310 K by the progesterone as in Fig. 3.

RMSD is helpful to measure the atomic coordinate in term of rooting the average value of square of these coordinates. It is also helpful to determine the conformational stability of macromolecular system using the atomic coordinates of the backbone atoms. The trajectory coordinates of backbone were used to compute the RMSD values. For a successful molecular docking, RMSD value should be least because it directly gives the deviation of mean atomic coordinates. Less the RMSD value of the complex means more will be the conformational stability of macromolecular system. Herein, RMSD values for Mpro of nCoV with progesterone/ testosterone were analyzed at 300, 310 and 325 K. It was found that RMSD values increases on increasing temperature. RMSD values at 300 K are under acceptable range and corroborating the successful docking. The RMSD values for both testosterone, progesterone and MPro of nCoV was found as 0.2 nm and 0.3 nm respectively. The result indicates better conformational stability of the complex between Mpro of nCoV and testosterone than with the progesterone. Result also indicate better conformational stability at low temperature in case both testosterone and progesterone as in Fig. 4. It was found that on increasing temperature RMSD increases means conformational stability of complex decreases. At 310 K, the RMSD values is little higher but are acceptable under the cellular circumstances.

RMSF is much more similar to the RMSD but it differs in sense that it uses individual residue flexibilities value for calculations. It

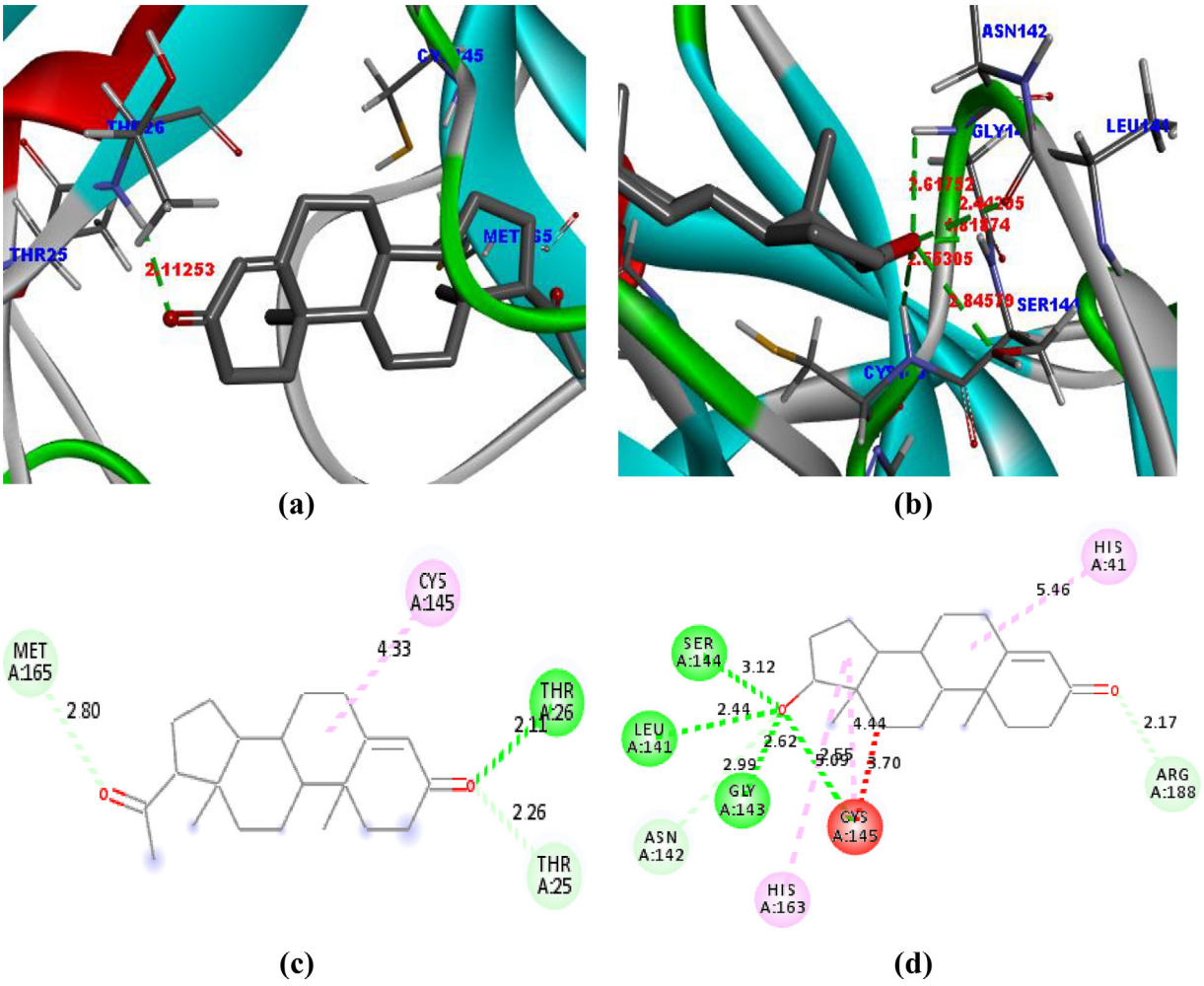

Fig. 2. 2D- and 3D- representation for the interaction between Mpro of nCoV with (a & c) progesterone and (b & d) testosterone after molecular docking.

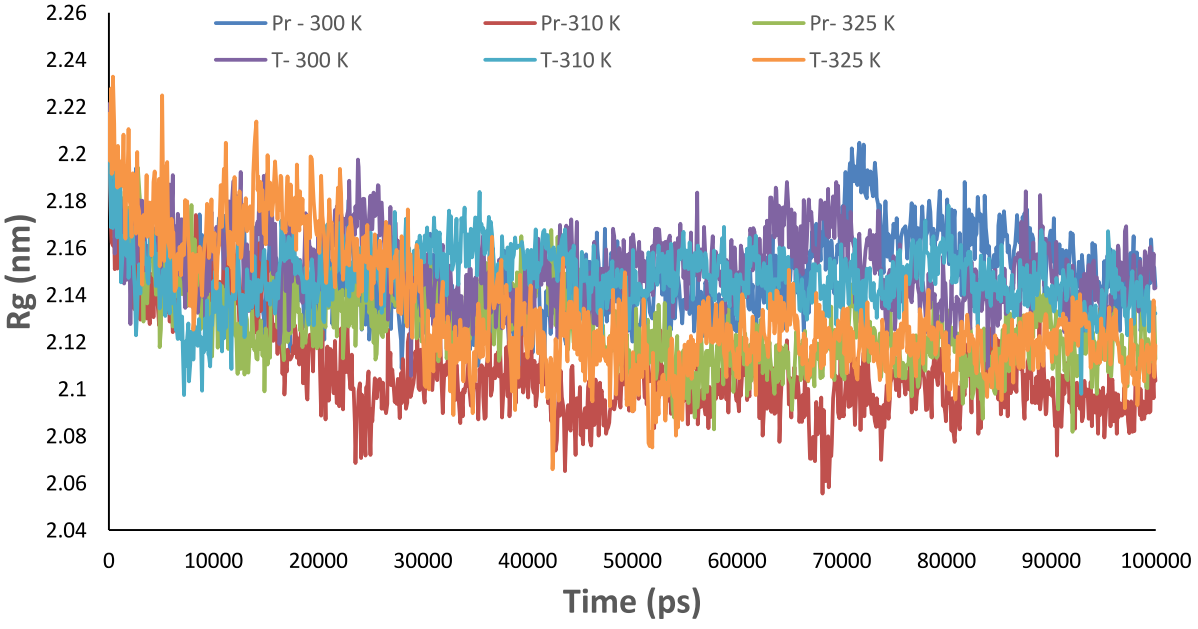

Fig. 3. Radius of gyration for the complex between MPro of nCoV and testosterone/ progesterone at 300, 310 and 325 K.

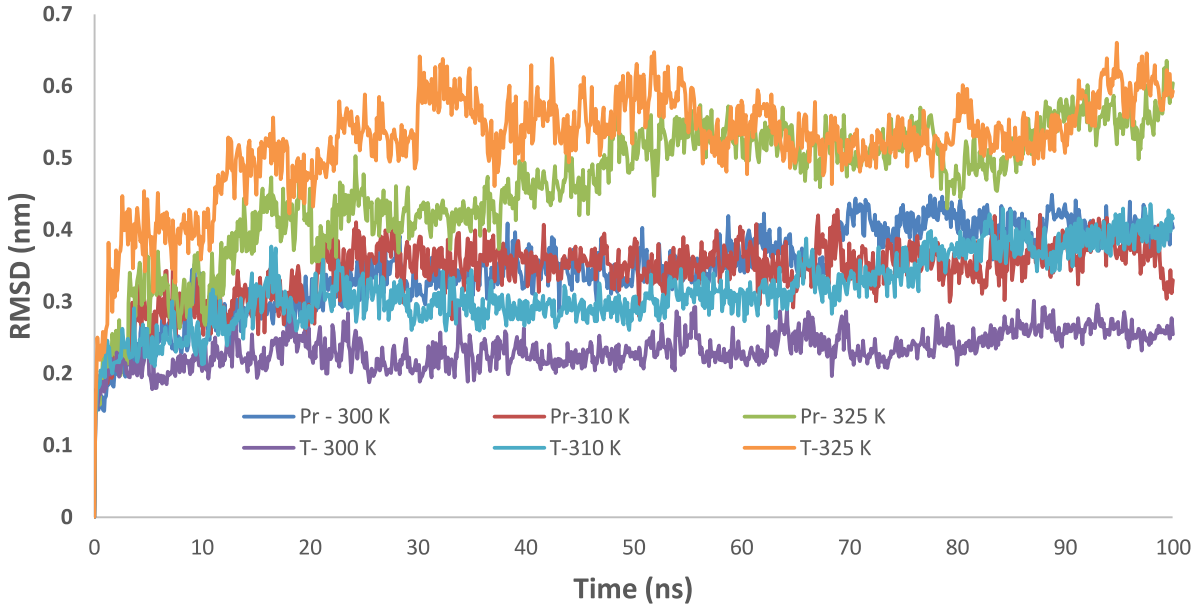

Fig. 4. RMSD fits to backbone for the complex between MPro of nCoV and testosterone/ progesterone at 300, 310 and 325 K.

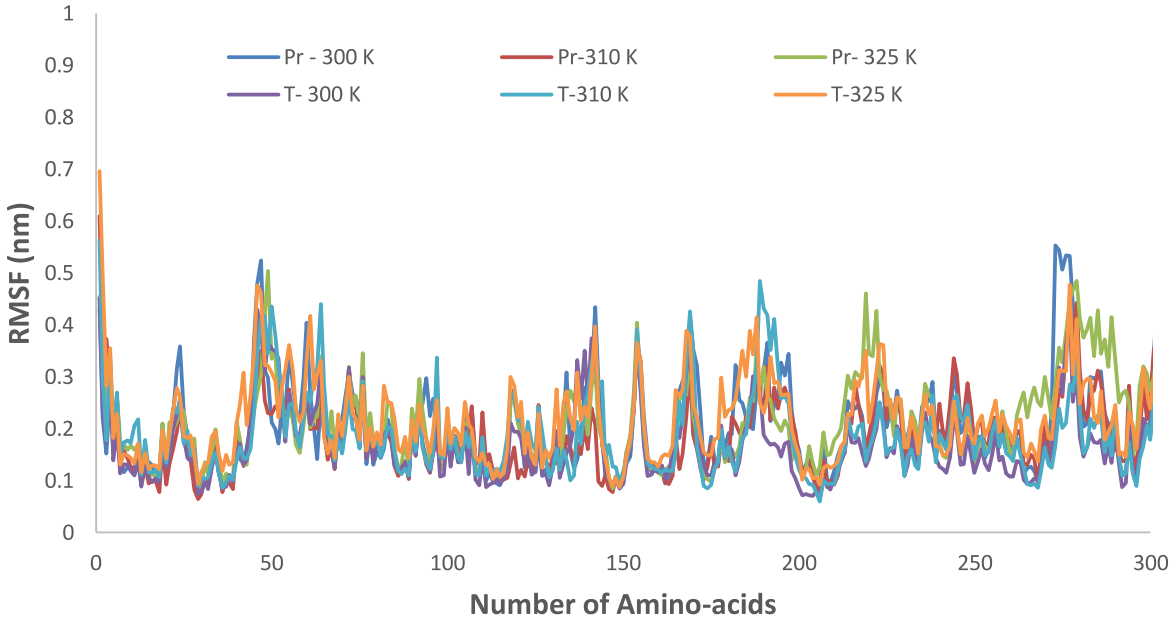

Fig. 5. RMSF fits to backbone for the complex between MPro of nCoV and testosterone/ progesterone at 300, 310 and 325 K.

can be used to define the conformational stability of the macromolecular system. Lesser the values of fluctuation indicates more conformational stability. However, variation in fluctuation value indicates the structural complexity within the macromolecular system. RMSF values for Mpro of nCoV with testosterone/ progesterone were plotted at 300, 310 and 325 K as given in Fig. 5. It is clear that some fluctuations occur in reason of 250 to 300 amino acid residues. However, the RMSF values remains in acceptable range i.e. near the 0.2 nm indicate stability of particular amino acid residues. Some instability recorded along amino acid residues value 175–225 and 250–300 at higher temperature. Fluctuations at binding cavity residues corroborates the successful docking. Herein, no significant effect of increase of temperature were observed.

Van der Waals interactions are hydrogen bond interactions are highly strong during the complex formation. Hydrogen bonds decide the proper anchoring of ligand in the receptor. More the number of hydrogen bonds indicates better anchoring of ligand within active binding cavity. The number of hydrogen bonds for Mpro of nCoV with testosterone and progesterone at 300, 310 and 325 K were analyzed. The number of hydrogen bonds and their persistence during the course of 100 ns simulation was analyzed at 300 K, 310 K and 325 K. Fig. 6 indicates that on increasing temperature number of hydrogen bonds increases. Initially, progesterone and Mpro of nCoV contains maximum three hydrogen bonds and then increases on increasing temperature. While in case of testosterone, it shows similar nature thaton increasing temperature, the number of hydrogen bonds decreases.

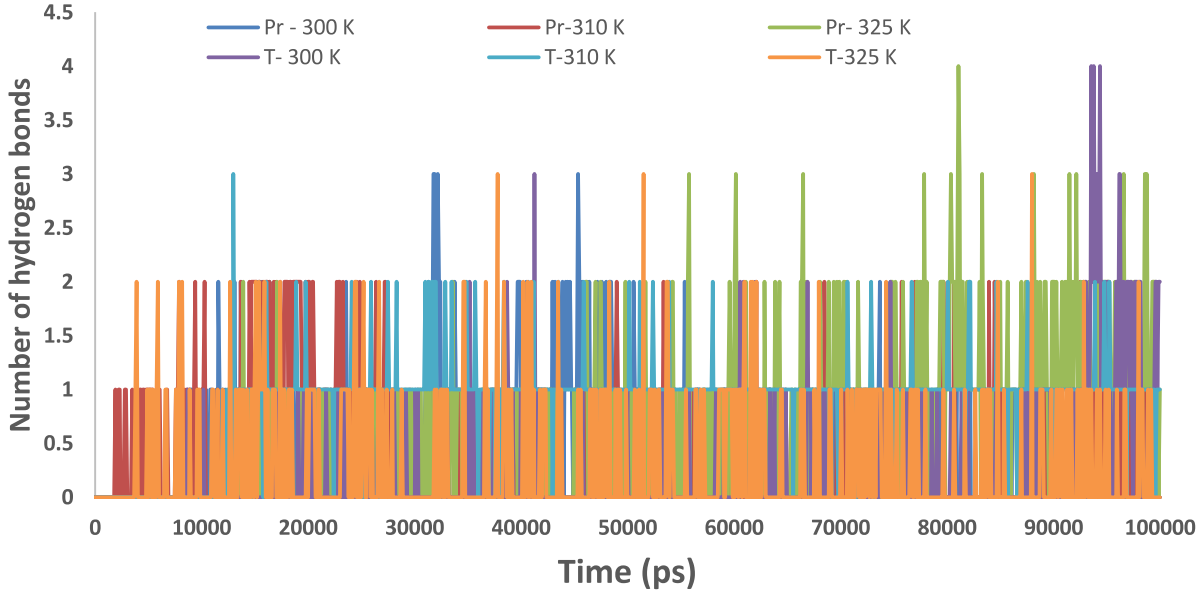

Fig. 6. Hydrogen bonds for the complex between MPro of nCoV and testosterone/ progesterone at 300, 310 and 325 K.

4. Conclusion

Herein, the interactions of testosterone and progesterone with MPro of nCoV were investigated with the help of molecular docking. The binding energy for the formation complex between the progesterone and testosterone with MPro are −86.05 and −91.84 kcal/mol respectively. From this, it can be understood that testosterone showed better binding with MPro of nCoV and thus, showed more inhibition. Then, the binding was further studied with molecular dynamics simulations at different temperatures, that is, 300, 310 and 325 K as the information obtained from molecular docking is not very reliable. It has been observed that the formations of complex between the Mpro of nCoV with testosterone/ progesterone is better at 300 than 310 and 325 K. Further, it is found that the binding is more effective with testosterone than the progesterone based on the Rg, RMSD, RMSF and H-bond trajectories.

Disclosure of potential conflicts of interest and informed consent

The corresponding authors declare that this manuscript is original, has not been published before and is not currently being considered for publication elsewhere. We further confirm that the order of authors listed in the manuscript has been approved by all of us. The authors also declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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.

Acknowledgements

Corresponding author, Prashant Singh dedicate this work in the memory his lovely teacher, ***late Dr. Vandana Uberoi***, Associate Professor of Chemistry, Acharya Narendra Dev College, University of Delhi, Delhi, India

References

[1] S.B. Chadchan, P. Popli, V.K. Maurya, R. Kommagani, The SARS-CoV-2 receptor, angiotensin-converting enzyme 2, is required for human endometrial stromal cell decidualization†, Biol. Reprod. 104 (2021), doi:10.1093/biolre/ioaa211.
[2] D.A. Abdelrheem, S.A. Ahmed, H.R. Abd El-Mageed, H.S. Mohamed, A.A. Rahman, K.N.M. Elsayed, S.A. Ahmed, The inhibitory effect of some natural bioactive compounds against SARS-CoV-2 main protease: insights from molecular docking analysis and molecular dynamic simulation, J. Environ. Sci. Heal. - Part A Toxic/Hazardous Subst. Environ. Eng. (2020) 55, doi:10.1080/10934529.2020.1826192.
[3] A. Frediansyah, F. Nainu, K. Dhama, M. Mudatsir, H. Harapan, Remdesivir and its antiviral activity against COVID-19: a systematic review, Clin. Epidemiol. Glob. Heal. 9 (2021), doi:10.1016/j.cegh.2020.07.011.
[4] S.Ş. Yavuz, S. Ünal, Antiviral treatment of covid-19, Turkish J. Med. Sci. (2020) 50, doi:10.3906/sag-2004-145.
[5] S. Pant, M. Singh, V. Ravichandiran, U.S.N. Murty, H.K. Srivastava, Peptide-like and small-molecule inhibitors against Covid-19, J. Biomol. Struct. Dyn. (2020), doi:10.1080/07391102.2020.1757510.
[6] 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 80- (2021) 371, doi:10.1126/science.abf4058.
[7] 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.
[8] J. Saraswat, P. Singh, R. Patel, A computational approach for the screening of potential antiviral compounds against SARS-CoV-2 protease: ionic liquid vs herbal and natural compounds, J. Mol. Liq. (2021) 326, doi:10.1016/j.molliq.2021.115298.
[9] L.C. Karlsson, A. Soveri, S. Lewandowsky, L. Karlsson, H. Karlsson, S. Nolvi, M. Karukivi, M. Lindfelt, J. Antfolk, Fearing the disease or the vaccine: the case of COVID-19, Pers. Individ. Dif. (2021) 172, doi:10.1016/j.paid.2020.110590.
[10] S.A. Khan, K. Zia, S. Ashraf, R. Uddin, Z. Ul-Haq, Identification of chymotrypsin-like protease inhibitors of SARS-CoV-2 via integrated computational approach, J. Biomol. Struct. Dyn. (2021) 39, doi:10.1080/07391102.2020.1751298.
[11] 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 pos-

sible hope for COVID-19: docking and molecular dynamics simulation studies, J. Mol. Liq. (2021) 335, doi:10.1016/j.molliq.2021.116185.
[12] A. Salonia, M. Pontillo, P. Capogrosso, S. Gregori, M. Tassara, L. Boeri, C. Carenzi, C. Abbate, D. Cignoli, A.M. Ferrara, W. Cazzaniga, I. Rowe, G.A. Ramirez, C. Tresoldi, J. Mushtaq, M. Locatelli, L. Santoleri, A. Castagna, A. Zangrillo, F. De Cobelli, M. Tresoldi, G. Landoni, P. Rovere-Querini, F. Ciceri, F. Montorsi, Severely low testosterone in males with COVID-19: a case-control study, Andrology. (2021), doi:10.1111/andr.12993.
[13] J. Durdiakova, D. Ostatnikova, P. Celec, Testosterone and its metabolites - modulators of brain functions, Acta Neurobiol. Exp. (Wars). 71 (2011) 434–454.
[14] S. Taraborrelli, Physiology, production and action of progesterone, Acta Obstet. Gynecol. Scand. 94 (2015) 8–16, doi:10.1111/aogs.12771.
[15] M. Schroeder, B. Tuku, D. Jarczak, A. Nierhaus, T. Bai, H. Jacobsen, M. Zickler, Z. Müller, S. Stanelle-Bertram, A. Meinhardt, J. Aberle, S. Kluge, G. Gabriel, The majority of male patients with COVID-19 present low testosterone levels on admission to intensive care in Hamburg, Germany: a retrospective cohort study, MedRxiv. (2020), doi:10.1101/2020.05.07.20073817.
[16] IRCT20150716023235N15, sex hormones in coronavirus, Http://Www.Who.Int/Trialsearch/Trial2.Aspx?TrialID=IRCT20150716023235N15. (2020).
[17] G. Pinna, Sex and COVID-19: a protective role for reproductive steroids, Trends Endocrinol. Metab. (2021) 32, doi:10.1016/j.tem.2020.11.004.
[18] C. Cattrini, M. Bersanelli, M.M. Latocca, B. Conte, G. Vallome, F. Boccardo, Sex hormones and hormone therapy during covid-19 pandemic: implications for patients with cancer, Cancers (Basel) 12 (2020), doi:10.3390/cancers12082325.
[19] D. Altın, İ. Yalçın, G. Khatib, M.D. Keleşoğlu, S. Akgöl, A.B. Önder, İ. Kahramanoğlu, T. Güvenal, S. Topuz, F. Demirkıran, Management of gynecological cancers in the COVID-19 era: a survey from Turkey, J. Turkish Ger. Gynecol. Assoc. 21 (2020), doi:10.4274/jtgga.galenos.2020.2020.0071.
[20] A.D. Makatsariya, G.C.D. Renzo, G. Rizzo, Regarding the evidence-based use of micronized progesterone, Reprod. Endocrinol. (2021), doi:10.18370/2309-4117.2020.55.105-108.
[21] O.M. Conneely, B. Mulac-Jericevic, F. DeMayo, J.P. Lydon, B.W. O'Malley, Reproductive functions of progesterone receptors, Recent Prog. Horm. Res. 57 (2002) 339–355, doi:10.1210/rp.57.1.339.
[22] J.T. Manning, B. Fink, Understanding COVID-19: digit ratio (2D:4D) and sex differences in national case fatality rates, Early Hum. Dev. (2020) 146, doi:10.1016/j.earlhumdev.2020.105074.
[23] G. Grandi, F. Facchinetti, J. Bitzer, The gendered impact of coronavirus disease (COVID-19): do estrogens play a role? Eur. J. Contracept. Reprod. Heal. Care. (2020) 25, doi:10.1080/13625187.2020.1766017.
[24] P.J. Niemann, H.V. Goldstein, Testosterone in COVID-19: friend or Foe? Endocrine (2021) 71, doi:10.1007/s12020-021-02623-2.
[25] S. Salciccia, M.L. Eisenberg, M. Maggi, S. Lai, C.M. Mastroianni, P. Pasculli, M.R. Ciardi, V. Canale, M. Ferro, G.M. Busetto, E. De Berardinis, G.P. Ricciuti, A. Sciarra, F. Del Giudice, Modeling the contribution of male testosterone levels to the duration of positive COVID testing among hospitalized male COVID-19 patients, Diagnostics (2021) 11, doi:10.3390/diagnostics11040581.
[26] J.C. André, Testostérone et Covid-19?, environnement, Risques et Sante. 19 (2020), doi:10.1684/ERS.2020.1445.
[27] S. Kalra, S. Bhattacharya, A. Kalhan, Testosterone in COVID-19 - foe, friend or fatal victim? Eur. Endocrinol. (2020) 16, doi:10.17925/ee.2020.16.2.88.
[28] S. Okçelik, COVID-19 pneumonia causes lower testosterone levels, Andrologia (2021) 53, doi:10.1111/and.13909.
[29] P. Shree, P. Mishra, C. Selvaraj, S.K. Singh, R. Chaube, N. Garg, Y.B. Tripathi, Targeting COVID-19 (SARS-CoV-2) main protease through active phytochemicals of ayurvedic medicinal plants–withania somnifera (ashwagandha), tinospora cordifolia (giloy) and ocimum sanctum (tulsi)–a molecular docking study, J. Biomol. Struct. Dyn. (2020), doi:10.1080/07391102.2020.1810778.
[30] A. Kumar, G. Choudhir, S.K. Shukla, M. Sharma, P. Tyagi, A. Bhushan, M. Rathore, Identification of phytochemical inhibitors against main protease of COVID-19 using molecular modeling approaches, J. Biomol. Struct. Dyn. (2021) 39, doi:10.1080/07391102.2020.1772112.
[31] R. Li, L.M. Macnamara, J.D. Leuchter, R.W. Alexander, S.S. Cho, MD simulations of tRNA and aminoacyl-tRNA synthetases: dynamics, folding, binding, and Allostery, Int. J. Mol. Sci. (2015) 16, doi:10.3390/ijms160715872.
[32] 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. (2020) 1219, doi:10.1016/j.molstruc.2020.128595.
[33] A. Grottesi, N. Bešker, A. Emerson, C. Manelfi, A.R. Beccari, F. Frigerio, E. Lindahl, C. Cerchia, C. Talarico, Computational studies of SARS-CoV-2 3cl-pro: insights from md simulations, Int. J. Mol. Sci. 21 (2020), doi:10.3390/ijms21155346.
[34] D. Kumar, K. Kumari, A. Jayaraj, P. Singh, Development of a theoretical model for the inhibition of nsP3 protease of Chikungunya virus using pyranooxazoles, J. Biomol. Struct. Dyn. (2020) 38, doi:10.1080/07391102.2019.1650830.
[35] M. Kumari, U.K. Singh, P. Singh, R. Patel, Effect of n-butyl-n-methylmorpholinium bromide ionic liquid on the conformation stability of human serum albumin, ChemistrySelect. 2 (2017). 10.1002/slct.201601477.
[36] 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 (2019) 4, doi:10.1002/slct.201803360.
[37] 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. (2020), doi:10.1080/07391102.2020.1752310.
[38] D. Kumar, P. Singh, A. Jayaraj, V. Kumar, K. Kumari, R. Chandra, V.K. Ramappa, Selective docking of pyranooxazoles against nsP2 of CHIKV eluted through isothermally and non-isothermally MD simulations, ChemistrySelect 5 (2020), doi:10.1002/slct.202000768.
[39] 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.
[40] 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 Bioinformatics 12 (2011), doi:10.1186/1471-2105-12-S1-S33.
[41] 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.
[42] E. Lindahl, P. Bjelkmar, P. Larsson, M.A. Cuendet, B. Hess, Implementation of the charmm force field in GROMACS: analysis of protein stability effects from correction maps, virtual interaction sites, and water models, J. Chem. Theory Comput. 6 (2010), doi:10.1021/ct900549r.
[43] C. Oostenbrink, A. Villa, A.E. Mark, W.F. Van Gunsteren, A biomolecular force field based on the free enthalpy of hydration and solvation: the GROMOS force-field parameter sets 53A5 and 53A6, J. Comput. Chem. (2004) 25, doi:10.1002/jcc.20090.
[44] M.J. Abraham, T. Murtola, R. Schulz, S. Páll, J.C. Smith, B. Hess, E. Lindah, Gromacs: high performance molecular simulations through multi-level parallelism from laptops to supercomputers, SoftwareX (2015) 1–2, doi:10.1016/j.softx.2015.06.001.
[45] A.W. Schüttelkopf, D.M.F. Van Aalten, PRODRG: a tool for high-throughput crystallography of protein-ligand complexes, Acta Crystallogr. Sect. D Biol. Crystallogr. (2004) 60, doi:10.1107/S0907444904011679.