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Original article

Potential role of nicotinamide analogues against SARS-COV-2 target proteins

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ABSTRACT

Background and objective: Coronavirus 2019 (COVID-19) is caused by 'severe acute respiratory syndrome coronavirus 2' (SARS-CoV-2), first reported in Wuhan, China in December 2019, which eventually became a global disaster. Various key mediators have been reported in the pathogenesis of COVID-19. However, no effective pharmacological intervention has been available to combat COVID-19 complications. The present study screens nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) as potential inhibitors of this present generation coronavirus infection using an in-silico approach.
Materials and methods: The SARS-CoV-2 proteins (nucleocapsid, proteases, post-fusion core, phosphatase, endoriboruclease) and ACE-2 protein were selected. The 2D structure of nicotinamide ribonucleoside and nicotinamide ribonucleotide was drawn using ChemDraw 14.0 and saved in .cdx format. The results were analyzed using two parameters: full fitness energy and binding free energy (ΔG).
Results: The full fitness energy and estimated ΔG values from docking of NM, and NMN with selected SARS-CoV-2 target proteins, ADMET prediction and Target prediction indicate the interaction of NR and NMN in the treatment of COVID-19.
Conclusions: Based on full fitness energy and estimated ΔG values from docking studies of NM and NAM with selected SARS-CoV-2 target proteins, ADME prediction, target prediction and toxicity prediction, we expect a possible therapeutic efficacy of NR in the treatment of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a global pandemic that has emerged as a major health crisis. As per WHO, COVID-19 has affected 215 countries & territories around the world till date. A growing number of evidence also suggests that viral infection is not only restricted to respiratory illnesses, but this virus eventually spreads out and triggers neuronal and cardiac complications (Geng et al., 2020, Wu et al., 2020). In a very short period, numerous efforts by researchers have been made to identify target sites along with exploration of therapeutic intervention in combating the prevention and treatment of COVID-19. These findings argue that numerous SARS-CoV-2 proteins such as fusion proteins, proteases,

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nucleocapsid proteins, ribose phosphatases, endoribonuclease and other free enzymes are involved in the pathogenesis of COVID-19 (Zhou et al., 2020, Prajapat et al., 2020). Unfortunately, till date, no promising therapeutic intervention is available for clinical use. Multiple off-label and investigational drugs, such as hydroxychloroquine, favipiravir, azithromycin, and lopinavir/ritonavir are in clinical practice against COVID-19. However, most of these drugs are associated with toxicity (Chary et al., 2020). In addition to these mainstay therapeutic options, corticosteroids are prescribed to reduce the inflammatory responses of the host in the lungs, which may lead to acute lung injury. Thus, the use of corticosteroids in the management of COVID-19 have their own limitations. Moreover, the safety and efficacy of convalescent plasma have not been assessed in robust clinical studies for the treatment of coronavirus infections. Therefore, it is the biggest challenge ever for physicians to provide effective therapy for their patients, as every physician is designing a therapy based on risk to benefit ratio. Thus, optimal management of patients with COVID-19 needs to be addressed. In this regard, we have explored various digital repositories searching for the most promising therapeutic interventions for the management of COVID-19.

It is worth mentioning here that SARS-CoV-2 greatly disturbs the NAD system by over-expressing the Poly (ADP-ribose) polymerase (PARP) genes (Heer et al., 2020). Depletion of NAD is associated with cellular injury and has been implicated in the aggravation of pulmonary, cardiac toxicity and diabetic complications (Wu et al., 2016, Harijith et al., 2017). Thus, it may be correlated with the higher mortality rate among those with pre-existing respiratory/cardiac disorders or diabetes mellitus. The world is looking toward an agent which not only reduces the SARS-CoV-2 associated mortality rate but can also act directly against SARS-CoV-2. The PARP inhibitors may reduce the mortality rate associated with SARS-CoV-2, especially in co-morbid patients. Interestingly, nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) has been noted to inhibit PARP overactivation and act as precursors of NAD. Thus, NR or NMN may be employed as warriors against SARS-CoV-2 associated mortality. However, our main objective is to explore the direct interaction of nicotinamide analogues with SARS-CoV-2 target proteins. Therefore, the present study was designed to conduct a virtual screening of NR and NMN against SARS-CoV-2 target proteins, absorption, distribution, metabolism, excretion and toxicity (ADMET) prediction and target prediction.

2. Materials and methods

2.1. Docking of nicotinamide ribonucleoside and nicotinamide mononucleotide on SARS-CoV-2 and ACE-2 proteins

2.1.1. Receptor preparation

The SARS-CoV-2 proteins (nucleocapsid, proteases, post-fusion core, phosphatase, endoriboruclease) and ACE-2 protein were selected based on a comprehensive understanding of the mechanism of entry and replication of the virus. Protein sequence data was collected from the protein data bank. Selected protein data along with their PDB ID are tabulated in Table 1.

Table 1
Targeted proteins of SARS-CoV-2.

Sr. No.	RCSB-PDP ID	Name of Protein
1	6M3M	SARS-CoV-2 nucleocapsid protein N-terminal RNA binding domain
2	6YB7	Protease
3	6W9C	Papain-like protease of SARS CoV-2
4	6LXT	Post fusion core of 2019-nCoV S2 subunit
5	6VXS	ADP ribose phosphatase of NSP3 from SARS CoV-2
6	6M0J	SARS-CoV-2 spike receptor-binding domain bound with ACE2
7	6VWW	NSP15 Endoribonuclease from SARS CoV-2
8	6Y2E	Free enzyme of the SARS-CoV-2 (2019-nCoV) main protease
9	1R42	Native Human Angiotensin-Converting Enzyme-Related Carboxypeptidase (ACE2)

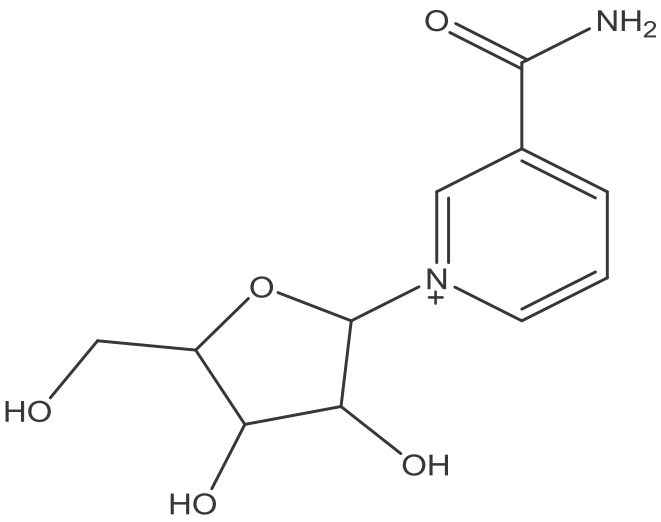


Fig. 1. Nicotinamide riboside.

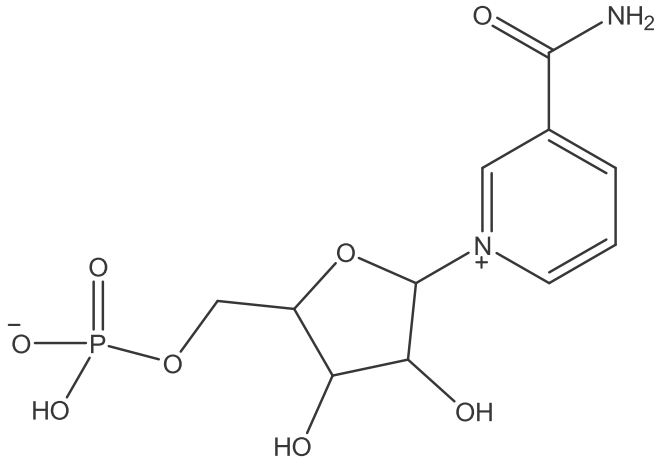


Fig. 2. Nicotinamide mononucleotide.

2.1.2. Ligand preparation

The 2D structure of nicotinamide ribonucleoside and nicotinamide ribonucleotide was drawn using ChemDraw 14.0 and saved in .cdx format (Fig. 1 and Fig. 2). The ligand file was then opened in open babel to convert the cdx format file to mol2 format. Hydrogen was added to the ligand using the Add hydrogen option and pH was set to standard physiological pH. The Mol2 format was used to save ligand files.

2.1.3. Docking

Docking is a molecular modeling technique that is used to predict how a protein interacts with ligands. Swissdock is a website where users can dock their respective ligands with proteins. Swissdock can compute the complete morphology and geometry, site and energy of ligands that interact with proteins. Predictions from Swissdock were analyzed by using UCSF Chimera. It is used for

interactive analysis and visualization of molecular structures. The results were analyzed using two parameters: full fitness energy and ΔG. Various energies of binding sites can be expressed by the following equation:

$$\Delta G = \Delta Gs_{ol} + \Delta G_{conf} + \Delta G_{int} + \Delta G_{roi} + \Delta G_{t/t} + \Delta G_{vib}$$

The elements contain solvent effects, variations in ligand and protein interaction, internal rotation, energy due to ligand–protein binding, complex formation due to ligand and receptor interaction, and variations in vibration modes that result in free energy formation. A potential interaction and stable system are based on low (negative) energy. Full fitness energy is the estimation of docking accuracy to estimate the fitness of a docking program by predicting the right ligand to bind with the receptor. Low energy conformations are chosen where the score of each pose acts as the fitness function (Grosdidier et al., 2011).

2.2. Adme prediction

ADME studies are very important to analyze the pharmacodynamics properties of ligands. Swiss ADME is a website that allows the user to predict the ADME properties of ligands. The server permits the user to enter SMILES information from PubChemor to draw their ligand. The structure of nicotine was drawn, converted to SMILES and various parameters such as drug-likeness rules (Ghose, Egan, Lipinski, Muegge and Veber), lipophilicity (WLOGP, iLOGP, XLOGP3, SILICOS-IT, MPLOGP, Log P_0/w), water solubility-Log S (SILICOS-IT, ESOL, Ali) and medicinal chemistry methods (Synthetic accessibility, Lead-likeness, Brenk, PAINS) were analyzed (Enmozhi et al., 2021, Daina et al., 2017).

2.3. Target prediction

The presence of cross-reactivity or phenotypical side effects produced by small biomolecules was determined by molecular target studies. The Swiss Target Prediction website was used to study the target prediction of nicotine. The structure of nicotine was drawn, then converted to SMILES and was analyzed (Keiser et al., 2007, Gfeller et al., 2014).

2.4. Toxicity prediction

The tolerance power of small molecules before clinical studies in animals as well as human models were predicted by toxicological prediction of small molecules. Toxicological effects such as AMES toxicity, LOAEL, T. pyriformis toxicity, skin toxicity, hERG-II inhibitor, Minnow toxicity, hERG-I inhibitor, LD50, hepatotoxicity, and human maximum tolerance dose were obtained from the online database, pkCSM (Zhang et al., 2020).

3. Results

3.1. Docking

The output of the docking analysis of nicotine with SARS-CoV-2 and ACE-2 proteins was the estimated ΔG (kcal/mol) and full fitness energy (kcal/mol) with which the ligand binds to the pocket of the receptor protein (Table 2). The results are summarized in Table 1 and the active receptor binding of NR and NMN are shown in Figs. 3–10.

3.2. Adme prediction

3.2.1. Nicotinamide riboside (NR)

The SWISSADME database was used for ADME prediction (Pires et al., 2015). The physicochemical characteristics of the drug molecule are 18 no. of heavy atoms, 4H bond donors, 5H bond acceptors, a molar refractivity of 59.81 and the TPSA parameter of the molecule is predicted at 116.89Å. Molecular lipophilicity values, iLOGP is −5.28, XLOGP3 −1.75, WLOGP is −2.64, MLOGP is −1.72, SILICOS-IT is −1.78, and Consensus P_0/w is-2.63.

The calculated water properties are ESOL −0.37, the solubility of $4.28e^{-01}$ mol/l and the drug belongs to the soluble class. pharmacokinetic data has predicted that the drug has low GI absorption, does not penetrate BBB, does not act as a P-gp substrate, and does not interact with cytochrome CYP1A2, CYP2D6, CYP2C19, CYP3A4 and CYP2C9. Log Kp value that reflects the reflects permeation kinetics of skin was found to be −9.10 cm/s.

The investigated compound complies with Lipinski's Rules to justify its potential as a drug-like compound. In addition, it also follows drug-likeness score rules, for example, Muegge, Veber, and Egan. It does not obey the Ghose score rules and has one violation with WLOGP < −0.4. Its bioavailability score is 0.55. Further, medicinal chemistry parameters support its lead likeness and its synthetic accessibility is found to be 3.56 (Fig. 11).

3.2.2. Nicotinamide mononucleotide (NMN)

For NMN, the SWISSADME database was used for ADME prediction. Molecular lipophilicity values are, XLOGP3 −3.40, iLOGP is −7.06, SILICOS-IT is-2.93, WLOGP is-2.08, MLOGP is-2.52, and Consensus P_0/w is −3.60. The physicochemical characteristics of the drug molecule are, 4H bond donors, 8H bond acceptors, 22 no. of heavy atoms, TPSA parameter of the molecule is found to be 176.06Å and the molar refractivity value of 69.19.

The calculated water-solubility properties are ESOL 0.36, the solubility of 4.28 mol/l and the drug belongs to the highly soluble class. The Log Kp value that reflects the permeation kinetics of skin was found to be −10.75 cm/s. Pharmacokinetic data has predicted that the drug has low GI absorption, does not penetrate the BBB,

Table 2
Full fitness and estimated ΔG values predicted for NR and NMN docked with target proteins by SwissDock.

	NR (Ligand)		NMN (Ligand)	
Protein	Full fitness energy (kcal/mol)	Estimated ΔG (Kcal/mol)	Full fitness energy (kcal/mol)	Estimated ΔG (Kcal/mol)
6M3M	**−2933.053**	−7.2609	−856.350	−7.8626
6YB7	−1177.909	−7.0915	−1318.895	−7.5934
6W9C	−1495.200	−6.6933	–	–
6LXT	**−5287.570**	−6.6915	−1280.262	**−13.8577**
6VXS	−1603.147	−7.2929	−1747.532	**−8.5855**
ACE2-1R42	−2971.375	−7.4008	−3115.608	**−9.1218**
6M0J	**−3315.379**	−6.9402	**−3458.019**	−6.6542
6VWW	**−3729.231**	**−8.6282**	**−3876.069**	**−8.8223**
6Y2E	−1133.363	−6.7545	−856.351	−7.3374

Values in bold means most potential targets for the compound.

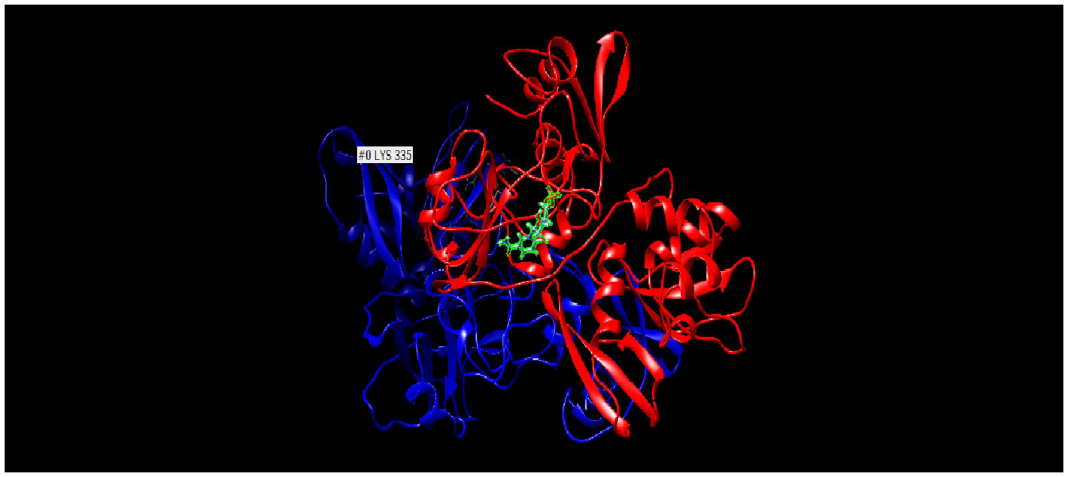


Fig. 3. Docking of 6M3M with NR.

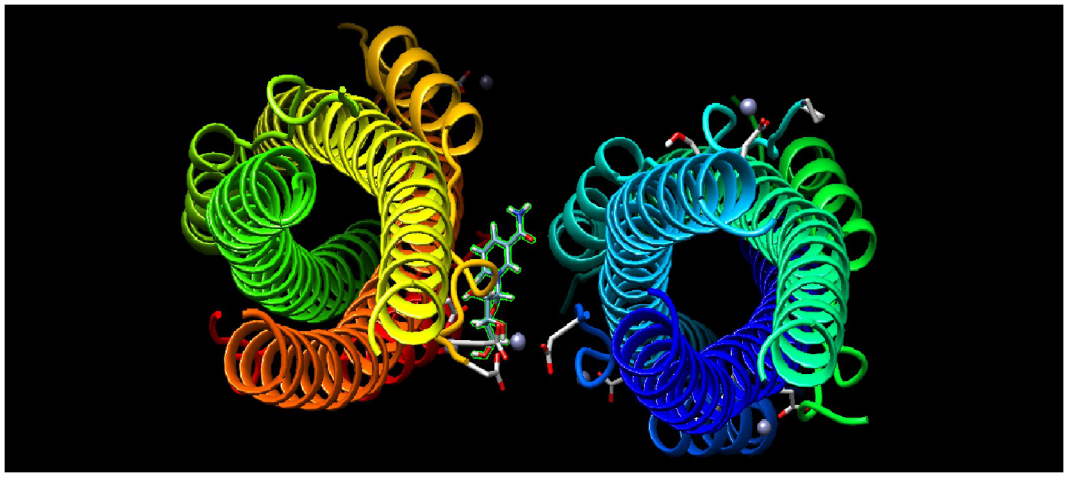


Fig. 4. Docking of 6LXT with NR.

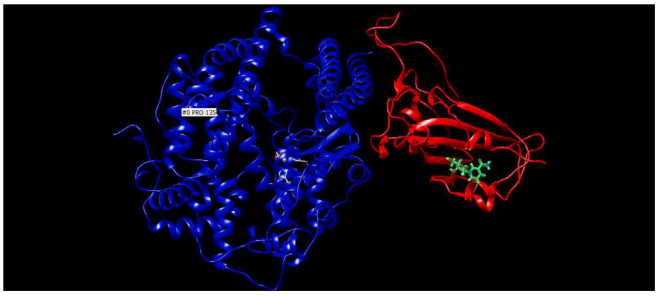


Fig. 5. Docking of 6M0J with NR.

acts as a P-gp substrate, and does not interact with cytochromes CYP2C19, CYP1A2, CYP3A4, CYP2D6 and CYP2C9.

The investigated compound complies with Lipinski's Rules to justify its potential as a drug. In addition, it does not follow drug-likeness score rules such as Egan, Ghose, and Veber with one violation each and does not obey Muegge's rule with two violations. Further, medicinal chemistry parameters are shown to be of no PAINS, Brenk with two alerts, lead likeness and its synthetic accessibility are found to be 4.13 (Fig. 11). Its bioavailability score is 0.11.

3.3. Target prediction

3.3.1. Nicotinamide riboside (NR)

Observations of target prediction analysis as shown on the web page were given in Fig. 12. The pie chart predicts 44% of protease, 24% enzymes, 8% of electrochemical transporter, 8% membrane receptor, 4% of phosphodiesterase, 4% oxidoreductase, 4% of lyase, 4% of Family A G protein-coupled receptor.

3.3.2. Nicotinamide mononucleotide (NMN)

Observations of Target prediction analysis as shown on the web page were given in Fig. 12. The pie chart shows 28% of enzymes, 20% of family A G protein-coupled receptor, 12% of unclassified proteins, 8% transferase, 8% kinase, 8% other cytosolic proteins, 4% of oxidoreductase, 4% of protease, 4% of lyase, and 4% of other nuclear proteins.

The output table for both NR and NMN consisting of Common Name, Target, Uniport ID, Target Class, ChEMBL-ID, Probability and known actives in 2D/3D are given in the Supplementary file. The possible binding sites where compounds easily bind with targets were screened using computational software and the predicted probability score was found to be very low.

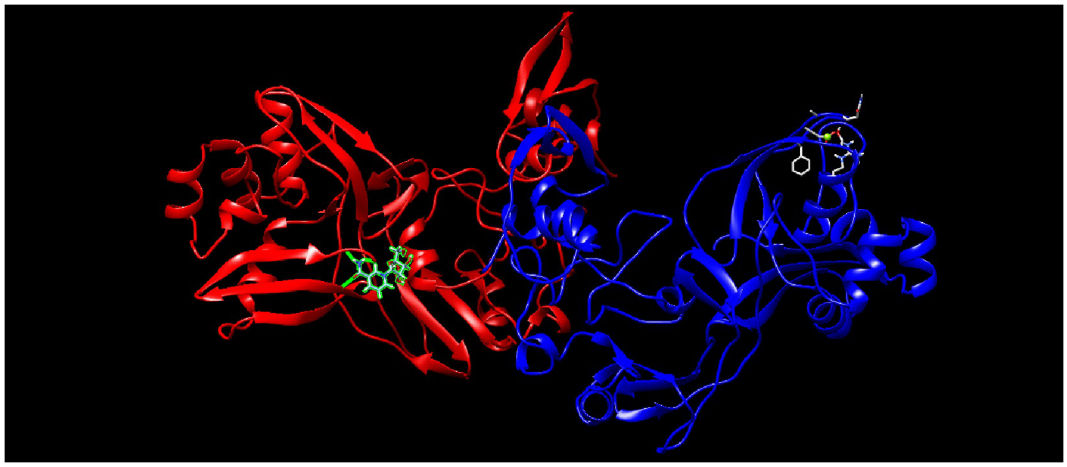


Fig. 6. Docking of 6VWW with NR.

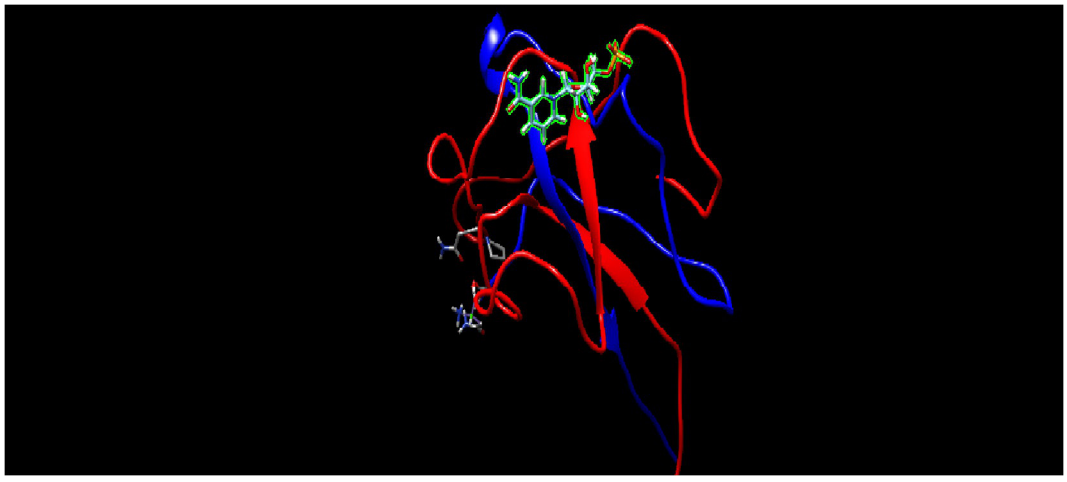


Fig. 7. Docking of 6M3M with NMN.

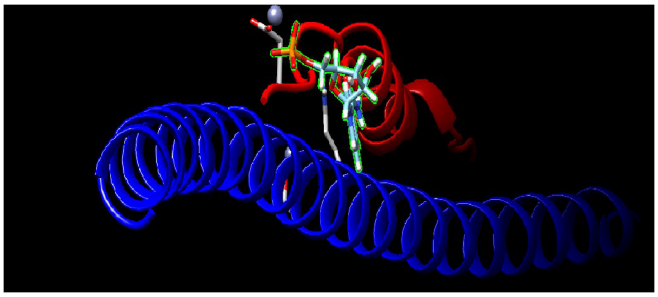


Fig. 8. Docking of 6LXT with NM.

3.4. Toxicity prediction

3.4.1. Nicotinamide riboside (NR)

The Toxicity prediction study reveals that the maximum tolerated human dose of NR is 0.493 log mg/kg/day and also shows that this is not associated with AMES toxicity and the ligand doesn't have any inhibitory action on hERG-I and II. The chronic oral toxicity (LOAEL) of NR was found to be 2.753 log mg/kg_bw/day and the acute oral toxicity (LD_{50}) was found to be 2.042 mol/kg, predicted to have no hepatotoxicity, no skin sensitization, T. pyriformis toxicity was found to be 0.276 log μg/L and Minnow toxicity was found to be 1.777 log mM.

3.4.2. Nicotinamide mononucleotide (NMN)

The Toxicity prediction study reveals that the maximum tolerated human dose of NMN is about 0.423 log mg/kg/day and also shows that this is not associated with AMES toxicity and the ligand doesn't have any inhibitory action on hERG-I and hERG-II. Chronic oral toxicity (LOAEL) for the ligand was found to be 2.996 log mg/kg_bw/day and acute oral toxicity (LD50) was found to be 1.851 mol/kg, predicted to have hepatotoxicity, no skin sensitization, T. pyriformis toxicity was found to be 0.285 log μg/L and Minnow toxicity was found to be 4.18 log mM.

4. Discussion

SARS-CoV-2 is a beta coronavirus with a single-stranded RNA genome. The virus utilizes the angiotensin-converting enzyme 2 (ACE2) of humans as a receptor to infect their cells. Homotrimeric spike glycoprotein (comprising a S1 subunit and S2 subunit in each spike monomer) on the envelope to bind to their cellular receptors. ACE2 binding induces the dissociation of the S1 with ACE2, prompting the S2 to transit from a metastable pre-fusion to a more

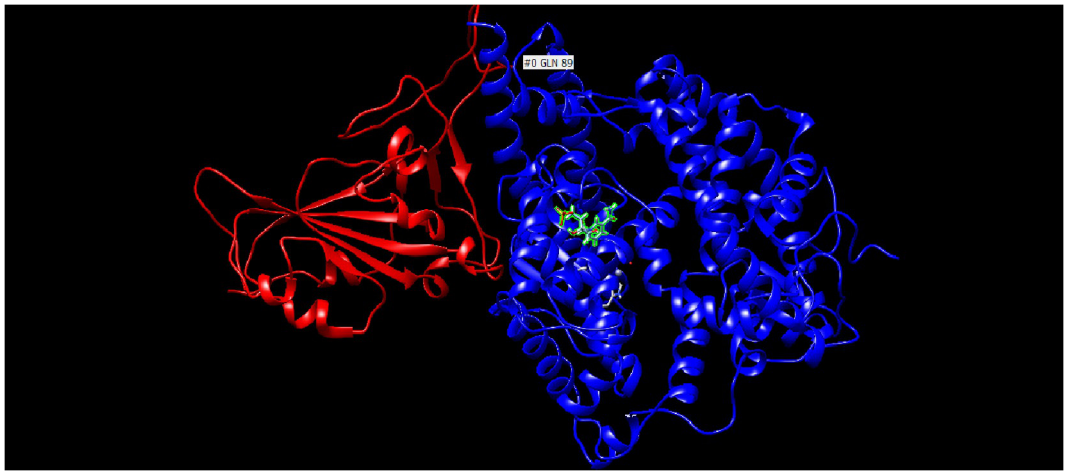


Fig. 9. Docking of 6M0J with NMN.

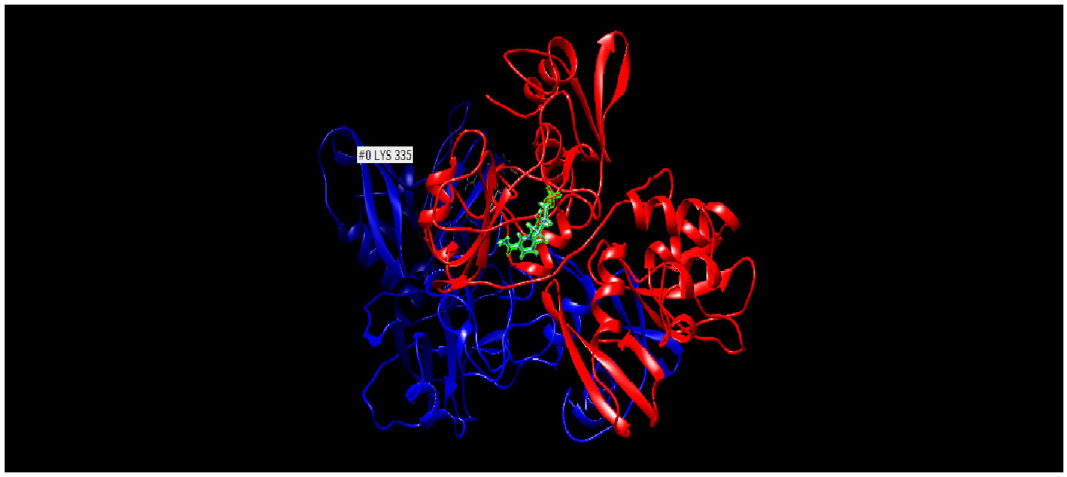
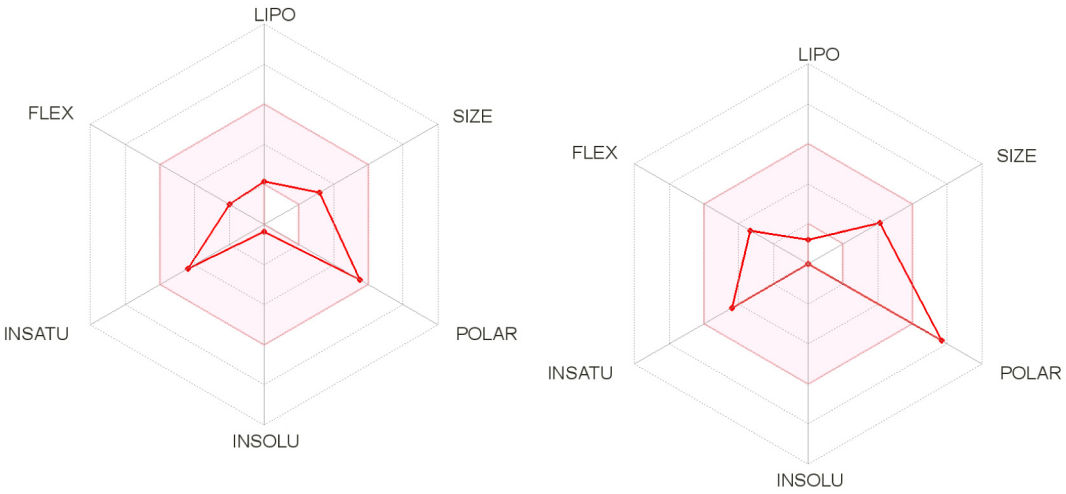


Fig. 10. Docking of 6VWW with NMN.



(ii)

Fig. 11. ADME Prediction of (i) NR and (ii) NMN.

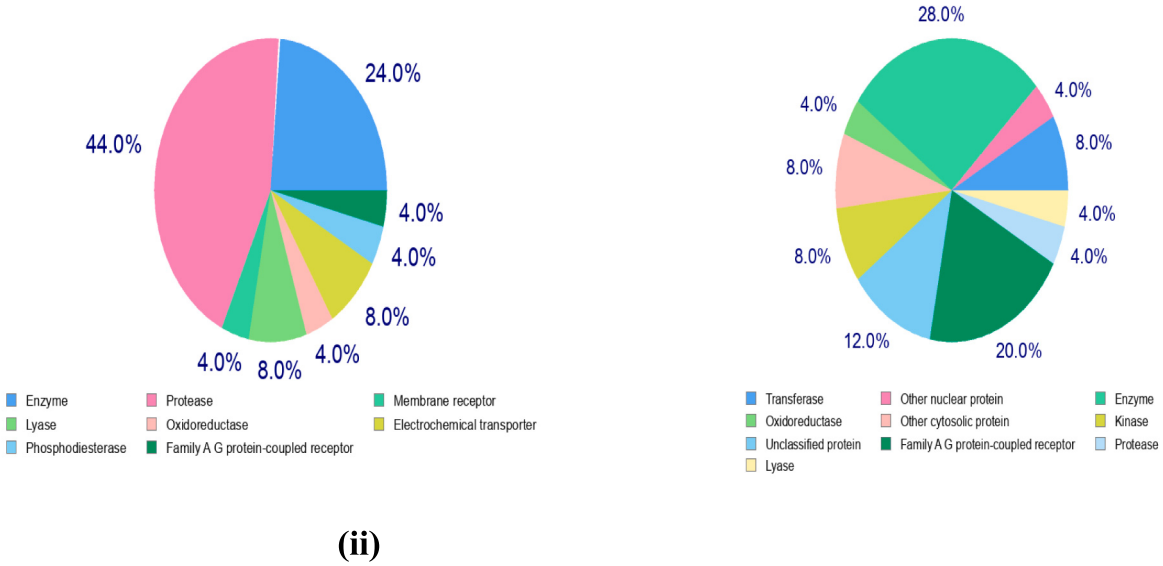


Fig. 12. Target Prediction of (i) NR and (ii) NMN.

stable post-fusion state that is essential for membrane fusion. Binding to the ACE2 receptor is a critical initial step for SARS-CoV to enter target cells. Therefore, the SARS-CoV-2 spike receptor-binding domain bound to ACE2 (6M0J) was selected. With the docking study, the free fitness energy for NR was found to be −3315.379 kcal/mol and for NMN was found to be −3458.019 kcal/mol, which shows similar values for NR and NMN. Almost the same results were observed for ΔG (for NR −6.9402 kcal/mol and for NMN −6.6542 kcal/mol).

After the initial step, the SARS-CoV spike (S) protein S2 subunit plays a key role in mediating virus fusion with and entry into the host cell. Thus, the post-fusion core of the 2019-nCoV S2 subunit (6LXT) is another target site for preventing infection. We also performed a docking study of NR and NMN with 6LXT. Free fitness energy was found to be −5287.570 kcal/mol and-1280.262 kcal/mol and ΔG was found to be −6.6915 kcal/mol and-13.8577 kcal/mol for NR and NMN respectively. The results indicate that NR is a potential candidate for the post-fusion core of the 2019-nCoV S2 subunit.

Further, N proteins have been considered as excellent drug-targeting candidates in other CoVs since the CoV N protein is a multifunctional RNA-binding protein necessary for viral RNA transcription and replication (Kang et al., 2020). In the present study, NR and NMN have been noted to dock on NTD (6M3M) with free energy of-7.2609 kcal/mol and −7.8626 kcal/mol, full fitness energy of-2933.053 kcal/mol and-856.350 kcal/mol suggesting the anti-COVID-19 potential of NR.

Among nonstructural proteins, NSP15 has been noted to be responsible for protein interference with the innate immune response and NSP15 degrades viral RNA to hide it from the host defenses. Thus, it is the biggest challenge for the immune system to combat the virus. The NSP15 Endoribonuclease from SARS CoV-2 (6VWW) was selected and the docking study revealed full fitness energy −3729.231 and −3876.069 and free energy −8.6282 and −8.8223, suggesting that NR and NMN are prospective agents against COVID-19.

The compound possesses excellent drug-ability properties. To assess the permeability of compounds through membranes and for their steadiness in the midst of strong/weak solute–solvent and also for solvent–solvent interactions, molar refractivity is considered a gold standard. TPSA refers to the transport properties of molecules. The high TPSA values of both compounds suggest they have poor blood–brain transport properties. The water solubility properties predict the compounds to be freely soluble. Both compounds were noted to have no inhibitory action on CYP1A2 and CYP2C19, thus they are not associated with the liver metabolism of drugs used in the treatment of malaria, ulcers, convulsions, and as anesthetics and sedatives. It is also observed that both the compounds do not interfere with CYP2D6 and thus will not inhibit the metabolism of β-blockers, anti-hypertensive, anti-depressants, and antiarrhythmics. In addition, there is no interaction with NSAIDs, anti-hypertensive, type2 diabetes, anti-clotting, and anti-seizure because the enzyme CYP2D9, which is associated with the metabolism of these drugs, has no interaction with NR and NMN. Further, both compounds do not inhibit CYP3A4, which is responsible for the metabolism of xenobiotics, fatty acids, steroidal drugs, and hormonal metabolism. Taken together, NR and NMN do not interfere with the metabolism of commonly used drugs.

The drug-likeness factor rules were obeyed by NR with only one violation, whereas NMN was found not to obey four of the five drug-likeness rules. It shows that prediction parameters justify NR as a drug in the biological system. As per the medicinal chemistry assessment of both the compounds, the zero value of PAINS signifies that NR and NMN are progressive compounds worthy of testing for biological assays. In general, any vitamin analogues, especially nicotinamide analogues, have been noted to be free from toxicity. However, our study reveals that NMN may be associated with hepatotoxicity. NR seems to have more interaction with targeted proteins, especially protease (44%) than NMN. So, NR possesses excellent drug-ability properties when compared to NMN.

5. Conclusions

Till date, no drug is available for clinical implementation based on its robust evaluation. But in the current clinical scenario, physicians are treating COVID-19 patients based on risk-to-benefit ratio. There is an urgent need to identify a potential therapeutic agent to manage this disease, and virtual studies are the only solution to explore the drug interaction with the molecular target sites of

COVID-19. Based on full fitness energy and estimated ΔG values from docking studies of NM, NAM with selected SARS-CoV-2 target proteins especially NSP15 Endoribonuclease and post fusion core of 2019-nCoV S2 subunit, ADME prediction, target prediction, and toxicity prediction, we expect the possible therapeutic efficacy of NR in the treatment of COVID-19. Further in-vitro experiments studies are required to justify the role of these compounds against SARS-CoV-2.

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sjbs.2021.09.072.

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