Smoking May Increase the Risk of COVID-19 Infection: Evidence from In Silico Analysis

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Authors’ contributions

This work was carried out in collaboration among all authors. Authors ML, AMM, and SK designed the study, wrote the protocol. Authors QMSJ, MK and JMA performed the experiments and statistical analysis. Authors AAA, MH and AF managed the literature searches and prepared the first draft of the manuscript. All authors read and approved the final manuscript.

ABSTRACT

Introduction: SARS-CoV2, first reported in December 2019 in Wuhan as COVID-19 causing respiratory illness, rapidly evolved into a pandemic owing to its very high infectivity. There is insufficient evidence about if and how smoking affects the risk of COVID-19 infection, and the reports on whether smoking increases or reduces the risk of respiratory infections, are
contradictory. Therefore, the current study was designed to determine the effects of nicotine consumption on the infectivity of COVID-19.

**Methods:** We performed *in silico* computer simulation-based study. The structures of SARS-CoV2 spike ectodomain, and its receptor ACE2, were obtained from PDB. The structure of nicotine and its metabolites NNK and NNAL were obtained from the PubChem chemical database. After optimization, they were interacted using AutoDock 4.2, to see the effect of nicotine, NNK, or NNAL presence on the docking of viral spike protein to its receptor ACE2.

**Results:** ACE2 vs spike protein interaction results were used as a control (ZDOCK score 1498.484, with four hydrogen bonds). The NNK+ACE2 vs spike protein docking formed 10 hydrogen bonds with the highest ZDOCK score of 1515.564. NNAL+ ACE2 vs spike protein interaction formed eleven hydrogen bonds with the ZDOCK score of 1499.371. Nicotine+ACE2 vs spike protein docking showed the lowest ZDOCK score of 1496.302 and formed 8 hydrogen bonds. Whereas, NNK+spike vs ACE2 interaction had a ZDOCK score of 1498.490 and formed eight hydrogen bonds. NNAL+spike vs ACE2 docking formed eleven hydrogen bonds with a ZDOCK score of 1498.482. And Nicotine+spike vs ACE2 interaction showed a ZDOCK score of 1498.488 and formed 9 hydrogen bonds.

**Conclusions:** The binding of nicotine to either spike of virus or its receptor ACE2 is not affecting the viral docking with the receptor. But binding of NNK, a metabolite of nicotine, is facilitating the viral docking with its receptor indicating that smoking may increase the risk of COVID-19 infection.

**Keywords:** Nicotine; SARS-CoV2; ACE2; NNK.

1. **INTRODUCTION**

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) has recently affected many people throughout the world. Till now there are 23, 406,044 cases have been reported and 809, 079 deaths happened since the beginning of the pandemic (Coronavirus Update (Live)). SARS-CoV2 is a positive-sense, single-stranded RNA virus, which belongs to the Coronavirus family. Previously also, two species of coronavirus namely SARS and MERS have caused disease in humans [1].

Most of the cases of COVID-19 are asymptomatic or self-limiting, but the clinical spectrum extends to severe pneumonia and acute respiratory distress syndrome (ARDS), a life-threatening condition requiring mechanical ventilation and intensive care support. The virus enters the body through the respiratory system, while the cellular entry is via the ACE2 receptor that is part of the renin-angiotensin system (RAS). The docking of viral spike protein to ACE2 receptor and their binding affinity plays a crucial role in viral infectivity. The ACE2-binding affinity of the spike protein of SARS-CoV2 is 10- to 20-fold higher than that of its ancestor SARS-CoV [2]. The S-protein ACE2 receptor interaction is the primary determinant for a coronavirus to infect a host cell and also administrates the tissue specificity of the virus. The docking is followed by a cascade of molecular events and finally, the virus gains access to the host cell’s cytosol and releases the viral genome into the cytoplasm [3].

Although the virus affects people of all ages but has high mortality in elderly people and those having comorbidities like diabetes, hypertension, etc. The effect of smoking on viral infectivity is debatable profoundly and is somewhat controversial. It is well recognized that smoking enhances the risk of respiratory infections (both bacterial and viral) and consequences are commonly worse in smokers and patients with chronic lung diseases [4]. Smoking has also been reported as a risk factor for both viral and bacterial infections and mortality due to MERS-CoV [5]. However, currently, there is rare evidence for the effects of smoke exposure on the risk of infection from SARS-CoV2 [6]. On the basis of previous findings, it is crucial to investigate the relationship between smoking and COVID-19.

To get in-sight of the issue, we employed the simulation methods to determine the effect of nicotine or its metabolites presence on the binding efficiency of the viral spike to its receptor ACE2.

2. **MATERIALS AND METHODS**

2.1 **Retrieval and Preparation of 3D Receptor Molecules**

3 dimensional (3D) structures of SARS-CoV2 spike ectodomain structure (open state) (PDB:
(6VYB) [7] generated by electron microscopy with the resolution 3.20 Å and single-particle was used as reconstruction method, also Native Human Angiotensin-Converting Enzyme-Related Carboxypeptidase (ACE2) 3D structure (PDB: 1R42) [8] build using X-ray diffraction method with the resolution of 2.2 Å were retrieved and downloaded from Protein Data Bank (PDB) (www.rcsb.org) [9]. HETATM and water molecules were removed from the downloaded PDB structural files using Discovery Studio Visualizer [10].

2.2 Preparation of Nicotine and Metabolites

PubChem chemical database maintained by National Center for Biotechnology Information (NCBI) (https://pubchem.ncbi.nlm.nih.gov/) was used to download NNK, NNAL, and Nicotine's physicochemical properties and structural information Table 1. 3D structures needed to prepare input essential PDB files as a ligand for AutoDock tool. Corina online molecular modeling software (https://www.mn-am.com/online_demos/corina_demo) was used to generate 3D structures from canonical SMILES IDs.

2.3 Energy Minimization

Energy minimization procedures can fix some nonstandard residues or atoms. Chimera’s molecular Modelling Toolkit (MMTK) was used to implement the Amber force-field parameter to minimize the 3D structures of both ligand and receptor molecules before molecular docking simulation [11,12].

2.4 In Silico Interaction Analysis

The docking methods are discussed in the following sections:

2.4.1 Nicotine/metabolites-receptor docking

In order to achieve significant results for the proposed hypothesis firstly, molecular interaction analysis of ligand and receptor molecules was performed by AutoDock 4.2 [13] to build nicotine/metabolites and receptors (with spike protein and ACE2) complexes. Using AutoDock utilities polar hydrogen atoms, Kollman united charges, and salvation parameters were added to the selected receptor molecules. Afterward, the ligand molecules i.e. NNK, NNAL, and nicotine were charged by Gasteiger. Grid box to cover spike protein’s target site was set to 40x40x40 Å in X, Y, and Z coordinate of a grid point with the values of 174.72, 247.475, and 219.195 respectively, and the values for a grid box to cover ACE2 target site was 60x60x60 Å followed by X, Y and Z coordinate of a grid point with the values of 80.401, 70.616 and 45.36 respectively for grid center with the default value of grid points spacing 0.375 Å. Lamarckian Genetic Algorithm (LGA) scoring function was used to perform ligand-receptor docking calculations [14]. The default LGA (10 runs) parameters mainly population size (ga_pop_size), energy evaluations (ga_num_generation), mutation rate, crossover rate and step size were set to 150, 2500000, 27000, 0.02, 0.8 and 0.2 Å, respectively [15]. After the execution of docking steps, the obtained 3D conformations of nicotine/metabolites-proteins complexes were generated for further analysis.

2.4.2 Protein-protein interaction

Furthermore, we extended docking experimentation followed by protein-protein docking to access the interaction pattern in three sets; a) between spike protein vs ACE2 as a control set. B) docking between nicotine/metabolites+ACE2 vs spike protein and c) nicotine/metabolites +spike protein vs ACE2. These were performed by the ZDOCK online server provided and maintained by Zhiping Weng’s lab (ZLAB) at the University of Massachusetts Medical School, USA. ZDOCK uses Fast Fourier Transform (FFT) algorithm as a scoring function for rigid-body protein–protein docking [16].

3. RESULTS

After performing protein-protein docking the obtained results are discussed in the following sections:

3.1 Nicotine/Metabolites+ACE2 vs Spike Protein Docking

For this analysis, we have set ACE2 vs spike protein interaction results as a control with the observed ZDOCK score 1498.484 with the formation of four hydrogen bonds Table 2. The prepared nicotine/metabolites+ACE2 complexes were docked with SARS-CoV2 spike protein.
The NNK+ACE2 vs spike protein docking formed 10 hydrogen bonds with the highest ZDOCK score 1515.564. The amino acid residues SER711, SER254, THR912, LYS600, ARG1107, SER602, SER254, SER711, GLY286, VAL1122, ASN601, GLU1092, GLY910, SER602, LYS26, SER254, SER708, GLN96 were involved in hydrogen bonding. LYS26 and GLN96 were forming hydrogen bonds with NNK Fig. 2a; Table 2.

NNAL+ACE2 vs spike protein interaction formed eleven hydrogen bonds with the ZDOCK score 1499.371. The amino acids SER711, SER254, THR912, LYS600, ARG1107, SER602, GLN96, SER254, SER711, GLY286, VAL1122, ASN601, GLU1092, GLN96, GLY910, SER602, SER254, SER708, LYS26 formed hydrogen bonds. Amino acid residues LYS26 and GLN96 have also formed hydrogen bonds with NNAL Fig. 2b; Table 2.

Nicotine+ACE2 vs spike protein docking shown the lowest ZDOCK score 1496.302 and formed 8 hydrogen bonds. Amino acid residues SER711, SER254, THR912, LYS600, ARG1107, SER602, GLN96, SER254, SER711, GLY286, VAL1122, ASN601, GLU1092, GLN96, GLY910, SER602, SER254, SER708, LYS26 formed hydrogen bonds. Amino acid residues LYS26 and GLN96 have also formed hydrogen bonds with Nicotine Fig. 2c; Table 2.

3.2 Nicotine/Metabolites+spike Protein vs ACE2 Docking

For this analysis, we have set spike protein vs ACE2 interaction results as a control with the observed ZDOCK score 1498.481 with the formation of 6 hydrogen bonds Table 2.

The prepared nicotine/metabolites+spike protein complexes were docked with human ACE2.

The Nicotine+spike vs ACE2 interaction showed 1498.488 ZDOCK score and formed eight hydrogen bonds. The amino acid residues ILE21, MET900, GLN24, MET900, SER218, VAL1122, THR29, TRP886, LEU79, ARG1091, ASN210, VAL1122, SER218, THR29 were involved in hydrogen bond interaction. Also, it was observed that THR29 formed two hydrogen bonds with NNK Fig. 3a; Table 2.

NNAL+spike vs ACE2 docking formed eleven hydrogen bonds with 1498.482 ZDOCK score. The amino acid residues ILE21, MET900, GLN24, MET900, SER218, VAL1122, THR29, ASN30, TRP886, LEU79, ARG1091, ASN210, VAL1122, SER218, THR29, ASN61, TYR28. It was observed that THR28, THR29, ASN30, and ASN61 were formed hydrogen bonds with NNAL Fig. 3b; Table 2.

The Nicotine+spike vs ACE2 interaction showed 1498.488 ZDOCK score and formed 9 hydrogen bonds. Amino acid residues ILE21, MET900, GLN24, MET900, SER218, VAL1122, THR29, TRP886, LEU79, ARG1091, ASN210, VAL1122, SER218, ASN61, THR63. Amino acid residues ASN61, THR63, and TYR269 were involved in hydrogen bond-forming Fig. 3c; Table 2.

4. DISCUSSION

Since the COVID-19 outbreak, a large number of deaths has been recorded and still counting. Several co-morbid conditions make people more vulnerable to viral infection and its severity.
Table 1. ZDOCK docking scores and description of H-bonds between ACE2 and spike protein without nicotine/metabolites (control), when NNK is bound to ACE2 (1), when NNAL is bound to ACE2 (2), and when nicotine is bound to ACE2 (3)

| S.No | Docking                  | ZDOCK score | No of hydrogen bonds | Length (Angstrom) | Residues involved in hydrogen bond formation |
|------|--------------------------|-------------|----------------------|-------------------|---------------------------------------------|
| **Control** | ACE2 receptor vs spike protein | 1496.484    | S:TRP866:NE1 - A:LEU79:O | 2.06762 | TRP866, LEU79, ARG1091, ASN210, VAL1122, SER218,ILE21,MET900, GLN24,MET900, SER218, VAL1122 |
| S:ARG1091:NE - A:ASN210:OD1 | 3.25551 | S:VAL1122:N - A:SER218:OG | 3.04752 |
| A:ILE21:N - S:MET900:SD | 3.0818 | A:GLN24:NE2 - S:MET900:SD | 3.00643 |
| A:SER218:OG - S:VAL1122:O | 3.29238 |
| **1** | NNK+ACE2 vs spike protein | 1515.564    | S:SER711:N - A:SER254:OG | 2.75732 | SER711,SER254, THR912,LYS600, ARG1107, SER602, SER254, SER711, GLY286, VAL1122, ASN601, GLU1092, GLY910, SER602, LYS26, SER254, SER708, GLN96 |
| S:THR912:OG1 - A:LYS600:O | 3.2363 | S:ARG1107:NE - A:SER902:OG | 2.93785 |
| A:SER254:OG - S:SER711:O | 3.09329 | A:GLY286:N - S:VAL1122:O | 2.84497 |
| A:ASN501:ND2 - S:GLU1092:O | 2.64375 |
| S:GLY910:CA - A:SER602:O | 1.98143 | A:LYS26:CA - N:UNK1:O7 | 3.43042 |
| A:SER254:CB - S:SER708:O | 2.42436 | N:UNK1:O1 - A:GLN96:OE1 | 3.40586 |
| **2** | NNAL+ACE2 vs spike protein | 1499.371    | S:SER711:N - A:SER254:OG | 2.75968 | SER711,SER254, THR912,LYS600, ARG1107, SER602, SER254, SER711, GLY286, VAL1122, ASN601, GLU1092, GLY910, SER602, LYS26, SER254, SER708, GLN96 |
| S:THR912:OG1 - A:LYS600:O | 3.23924 | S:ARG1107:NE - A:SER902:OG | 2.93963 |
| A:GLN96:NE2 - N:UNK1:N14 | 2.99797 | A:SER254:OG - S:SER711:O | 3.09173 |
| A:GLY286:N - S:VAL1122:O | 2.84615 | A:ASN501:ND2 - S:GLU1092:O | 2.64569 |
| N:UNK1:O13 - A:GLN96:OE1 | 2.56786 | S:GLY910:CA - A:SER602:O | 1.97993 |
| A:SER254:CB - S:SER708:O | 2.42689 | A:LYS26:NZ - N:UNK1 | 4.16422 |
| **3** | Nicotine+ ACE2 vs spike protein | 1496.302    | S:SER711:N - A:SER254:OG | 2.80476 | SER711,SER254, THR912,LYS600, ARG1107, SER602, SER254, SER711, GLY286, VAL1122, ASN601, GLU1092, GLY910, SER602, SER254, SER708, LYS26 |
| S:THR912:OG1 - A:LYS600:O | 3.28415 | S:ARG1107:NE - A:SER902:OG | 2.93963 |
| A:GLY286:N - S:VAL1122:O | 2.84615 | A:ASN501:ND2 - S:GLU1092:O | 2.64569 |
| A:GLY910:CA - A:SER602:O | 2.00148 | A:SER254:CB - A:SER602:O | 3.21864 |
| S.No | Docking | ZDOCK score | No of hydrogen bonds | Length (Angstrom) | Residues involved in hydrogen bond formation |
|------|---------|-------------|---------------------|------------------|---------------------------------------------|
| **Control** | ACE2 receptor vs spike protein ligand | 1498.481 | | | |
| | | | **ILE21N -- S:MET900:SD** | 3.08191 | **ILE21,MET900,GLN24,MET900,SER218,VAL1122,** |
| | | | **A:GLN24:NE2 -- S:MET900:SD** | 3.00593 | **TRP886,LEU79,ARG1091,ASN210,** |
| | | | **A:SER218:OG -- S:VAL1122:O** | 3.29263 | **VAL1122,** |
| | | | **S:TRP866:NE1 -- A:LEU79:O** | 2.06779 | |
| | | | **S:ARG1091:NE -- A:ASN210:OD1** | 3.2554 | |
| | | | **S:VAL1122:N -- A:SER218:OG** | 3.0477 | |
| **1** | NNK+spike vs ACE2 | 1498.490 | | | |
| | | | **ILE21N -- S:MET900:SD** | 3.08191 | **ILE21,MET900,GLN24,** |
| | | | **A:GLN24:NE2 -- S:MET900:SD** | 3.00593 | **MET900,SER218,VAL1122,** |
| | | | **A:SER218:OG -- S:VAL1122:O** | 3.29263 | **THR29,** |
| | | | **S:THR29:N -- N:UNK1:O7** | 3.37549 | |
| | | | **S:TRP866:NE1 -- A:LEU79:O** | 2.06779 | |
| | | | **S:ARG1091:NE -- A:ASN210:OD1** | 3.2554 | |
| | | | **S:VAL1122:N -- A:SER218:OG** | 3.0477 | |
| | | | **N:UNK1:C9 -- S:THR29:O** | 3.10571 | |
| **2** | NNAL+spike vs ACE2 | 1498.482 | | | |
| | | | **ILE21N -- S:MET900:SD** | 3.08191 | **ILE21,MET900,GLN24,MET900,** |
| | | | **A:GLN24:NE2 -- S:MET900:SD** | 3.00593 | **SER218,VAL1122,** |
| | | | **A:SER218:OG -- S:VAL1122:O** | 3.29263 | **THR29,** |
| | | | **S:THR29:N -- N:UNK1:O13** | 3.36767 | |
| | | | **S:ASN30:N -- N:UNK1:O15** | 3.00876 | **ASN61,THR28,** |
| | | | **S:TRP866:NE1 -- A:LEU79:O** | 2.06779 | |
| | | | **S:ARG1091:NE -- A:ASN210:OD1** | 3.2554 | |
| | | | **S:VAL1122:N -- A:SER218:OG** | 3.0477 | |
| | | | **N:UNK1:O13 -- S:THR29:O** | 2.77987 | |
| | | | **N:UNK1:O13 -- S:ASN61:OD1** | 2.60479 | |
| | | | **N:UNK1:C1 -- S:THR28:O** | 2.95107 | |
| **3** | Nicotine+spike vs ACE2 | 1498.488 | | | |
| | | | **ILE21N -- S:MET900:SD** | 3.08191 | **ILE21,MET900,GLN24,MET900,** |
| | | | **A:GLN24:NE2 -- S:MET900:SD** | 3.00593 | **SER218,VAL1122,** |
| | | | **A:SER218:OG -- S:VAL1122:O** | 3.29263 | **THR29,** |
| | | | **S:TRP866:NE1 -- A:LEU79:O** | 2.06779 | **TRP886,LEU79,** |
| | | | **S:ARG1091:NE -- A:ASN210:OD1** | 3.2554 | **ARG1091,ASN210,** |
| | | | **S:VAL1122:N -- A:SER218:OG** | 3.0477 | **VAL1122,** |
| | | | **N:UNK1:C1 -- S:ASN61:OD1** | 2.99049 | **SER218,** |
| | | | **N:UNK1:C1 -- S:THR63:OG1** | 3.05123 | **ASN61,** |

Table 2. ZDOCK docking scores and description of H-bonds between ACE2 and spike protein without nicotine/metabolites (control), when NNK is bound to spike protein (1), when NNAL is bound to spike protein (2), and when nicotine is bound to spike protein (3)
Fig. 2. 3D visualization of nicotine/metabolites+ACE2 (purple color) vs spike protein (light green color) interaction (a) NNK (shown by red color) +ACH2 vs spike (b) NNAL (shown by black color)+ACE2 vs spike and (c) Nicotine (shown by dark green color)+ACE2 vs spike protein. Blue dotted lines are showing hydrogen bonds.

Fig. 3. 3D visualization of nicotine/metabolites+ spike protein (light green color) vs ACE2 (purple color) interaction (a) NNK (shown by red color) +ACE2 vs spike (b) NNAL (shown by black color) +ACE2 vs spike and (c) Nicotine (shown by dark green color) +ACE2 vs spike protein. Blue dotted lines are showing hydrogen bonds.
Cigarette smoking has already been linked with several disease conditions like hypertension, cardiovascular disorders, diabetes, and even lung cancer. Smoking increases the risk of respiratory infections (both bacterial and viral) and symptoms are generally severe in smokers [4]. Smoking has also been reported as a risk factor both for infection and mortality due to MERS-CoV [5]. WHO published a report on 30 June 2020 after meta-analyses concluding that smoking could be associated with enhanced severity of disease and death in hospitalized COVID-19 patients [17]. Though, the reports are contradictory concerning the vulnerability of smokers to COVID-19 infection. We explored the facts at a molecular level with the available computational methods like Auto Dock for molecular docking and ZDOCK tool for Protein-Protein interaction etc.

We explored whether the presence of nicotine or its metabolite NNK and NNAL affects (positively or negatively) the binding efficiency of SARS-CoV2 spike protein with its receptor ACE2.

The interaction of spike protein with ACE2 using ZDOCK scored 1498.484 with the formation of four hydrogen bonds Table 2. This can be considered a non-smoker (absence of nicotine or its metabolites) condition. Whereas, in smokers, the presence of nicotine or its metabolites may represent two possible scenarios:

(a) Nicotine or its metabolites may bind to the ACE2 receptor. In this condition, the NNK+ACE2 vs spike protein docking formed 10 hydrogen bonds with the highest ZDOCK score 1515.564. NNAL+ACE2 vs spike protein interaction formed eleven hydrogen bonds with the ZDOCK score 1499.371. Whereas, Nicotine+ACE2 vs spike protein docking shown the lowest ZDOCK score 1496.302 and formed 8 hydrogen bonds Table 2.

(b) Nicotine or its metabolites may bind to spike protein of SARS-CoV2. In this condition, NNK+spike vs ACE2 interaction shown 1498.490 ZDOCK score and formed eight hydrogen bonds. NNAL+spike vs ACE2 docking formed eleven hydrogen bonds with 1498.482 ZDOCK score. Whereas, nicotine+spike vs ACE2 interaction shown 1498.488 ZDOCK score and formed 9 hydrogen bonds Table 2.

A comparison of smokers (a and b) with non-smokers conditions very clearly revealed that the binding of nicotine and NNAL to ACE2, does not affect the docking of the viral spike to the ACE2 receptor. Also, the binding of nicotine and its metabolite to spike protein does not affect the docking of the viral spike to its receptor ACE2. Whereas, NNK when bound to ACE2, significantly facilitate the viral spike docking to ACE2. This strongly advocates the higher vulnerability of smokers to viral infection.

A recent computational study has demonstrated that structural changes in human ACE2 can enhance the binding capabilities of SARS-CoV2 spike protein [18]. The binding of NNK to ACE2 probably triggers such structural alterations and promotes viral docking leading to increased subsequent internalization of the viral genome. Not only this, the transcriptomic data sets investigation revealed that pulmonary ACE2 gene expression is increased due to cigarette smoke inhalation consequently enhancing binding to AEC2 as well as easy entry of SARS-CoV2 [19]. In rodents also, cigarette smoke exposure is reported to enhance inflammatory signaling and increase the expression of ACE2 in the respiratory tract, thus making it more susceptible to the COVID-19 [20]. Studies with Middle East Respiratory Syndrome (MERS) also indicated that patients with a smoking history have poor pulmonary functions and were highly affected by the MERS coronavirus [21,22].

5. CONCLUSION

The computational structural analysis provides the quickest way to predict and explore the possible mechanism of biomolecular interactions. During COVID-19 the computational analysis proved as a useful tool in the screening and designing of drugs and vaccines against COVID-19. Our study using structural analysis methodology predicted the effects of cigarette smoke nicotine or its metabolites on human ACE2. It could be useful for future molecular investigations related to COVID-19 infection and smokers. The molecular investigations on the present lines may help in better understanding the effect of cigarette smoking and its role on the severity of COVID-19 infection. Our study provides a platform and clue for the designing of wet-lab experimentation (in vivo and in vitro) and opens a venue for further in-depth exploration.
DISCLAIMER
The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by the personal efforts of the authors.

CONSENT
It's not applicable.

ETHICAL APPROVAL
It's not applicable.

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COMPETING INTERESTS
Authors have declared that no competing interests exist.

REFERENCES
1. Known drugs and small molecules in the battle for COVID-19 treatment. Genes Dis. 2020;7(4):528–534. Published online 2020 Jun 20. DOI: 10.1016/j.gendis.2020.06.007.
2. Wrapp D, Wang N, Corbett KS. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020; 367:1260e1263.
3. Bosch BJ, Martina BE, Van Der Zee R. Severe acute respiratory syndrome coronavirus (SARS-CoV) infection inhibition using spike protein heptad repeat-derived peptides. Proc Natl Acad Sci U S A. 2004;101:8455e8460.
4. Arcavi L, Benowitz NL. Cigarette Smoking and Infection. Arch Intern Med. 2004;164(20):2206.
5. Park JE, Jung S, Kim A. MERS transmission and risk factors: a systematic review. BMC Public Health. 2018;18(1):574.
6. Vardavas CI, Nikitara K. COVID-19 and smoking: A systematic review of the evidence. Tob Induc Dis. 2020;18:20.
7. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D. Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 2020;181(2):281-292.e6. DOI:10.1016/j.cell.2020.02.058
8. Towler P, Staker B, Prasad SG, Menon S, Ryan D, Tang J, Parsons T, Fisher M, Williams D, Dales NA, Patane MA, Pantoliano MW. Native Human Angiotensin Converting Enzyme-Related Carboxypeptidase (ACE2). J Biol Chem. 2004;279:17996-18007
9. Berman HM, Westbrook J, Feng Z, Gilliland G, Bhat TN, Weissig H, Shindyalov IN, Bourne PE. The Protein Data Bank Nucleic Acids Research. 2000; 28:235-242.
10. Dassault Systèmes BIOVIA, Discovery studio visualizer, San Diego: Dassault Systèmes; 2020.
11. Pettersen EF, Goddard TD, Huang CC, Couch GS, Greenblatt DM, Meng EC, Ferrin TE. UCSF Chimera—a visualization system for exploratory research and analysis. J Comput Chem. 2004 Oct;25(13):1605-12.
12. Salomon-Ferrer R, Case DA, Walker RC. An overview of the Amber biomolecular simulation package. WIREs Comput. Mol. Sci. 2013;3:198-210.
13. Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS and Olson AJ. Autodock4 and AutoDockTools4: automated docking with selective receptor flexibility. J. Computational Chemistry. 2009;16:2785-91.
14. Goodsell DS, Morris GM, Olson AJ. Automated docking of flexible ligands: applications of AutoDock. J Mol Recognit. 1996; 9(1):1-5. DOI:10.1002/sici1099-1352(199601):9:1<1::aid-jmr241>3.0.co;2-6
15. Haneef M, Lohani M, Dhasmana A, Jamal QM, Shahid SM, Firdaus S. Molecular Docking of Known Carcinogen 4- (Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone
(NNK) with Cyclin Dependent Kinases towards Its Potential Role in Cell Cycle Perturbation. Bioinformation. 2014;10(8):526-532. Published 2014 Aug 30. DOI:10.6026/97320630010526

16. Pierce BG, Wiehe K, Hwang H, Kim BH, Vreven T, Weng Z. ZDOCK Server: Interactive Docking Prediction of Protein-Protein Complexes and Symmetric Multimers. Bioinformatics. 2014;30(12):1771-3.

17. WHO | Middle East Respiratory Syndrome Coronavirus (MERS-CoV). WHO, World Health Organization; 2013. Available: http://www.who.int/emergencies/mers-cov/en/. 23 Aug. 2020.

18. Hussain M, Jabeen N, Raza F. Structural variations in human ACE2 may influence its binding with SARS-CoV-2 spike protein [published online ahead of print, 2020 Apr 6]. J Med Virol; 2020. DOI:10.1002/jmv.25832

19. Cai G, Bossé Y, Xiao F, Kheradmand F, Amos CI. Tobacco Smoking Increases the Lung Gene Expression of ACE2, the Receptor of SARS-CoV-2. Am J Respir Crit Care Med. 2020;201(12):1557-1559. DOI:10.1164/rccm.202003-0693LE

20. Smith JC, Sausville EL, Girish V. Cigarette Smoke Exposure and Inflammatory Signaling Increase the Expression of the SARS-CoV-2 Receptor ACE2 in the Respiratory Tract. Dev Cell. 2020;53(5):514-529.e3. DOI:10.1016/j.devcel.2020.05.012

21. Nam HS, Park JW, Ki M, Yeon MY, Kim J, Kim SW. High fatality rates and associated factors in two hospital outbreaks of MERS in Daejeon, the Republic of Korea,International Journal of Infectious Diseases. Volume 58, 2017;37-42, ISSN1201712, Available:https://doi.org/10.1016/j.ijid.2017.02.008.

22. Available:https://www.who.int/news-room/commentaries/detail/smoking-and-covid-19

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