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Vitamins A, D and E: prospects in SARS- CoV2 therapeutics

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Abstract : The SARs-Cov2 pandemic commonly known as Covid-19 has affected the word like never before in the recent past. At present a highly efficient drug is yet to be found which can control and completely stop further damage to human health and world economy. A need for stopping further spread of this pandemic in minimal time using drug repurposing without long term experiments has surfaced. This study was thus designed to find possible targets for covid-19 therapeutics. We did docking (Insilco) study to find the usefulness of three commonly used vitamins for this purpose. Spike receptor binding domain without receptor was chosen as the target and the Vitamins A, D and E were the ligands. We found that the vitamins A and D were good candidates for covid19 therapeutics.

Key words: SARs-Cov2 pandemic, Covid-19, Vitamins A, D and E

INTRODUCTION

In the past century 1918 influenza and human immunodeficiency virus (HIV) pandemics have already baffled the world. In the present century the severe acute respiratory syndrome (SARS-CoV) and Middle Eastern respiratory syndrome corona virus (MERS-CoV) had already challenged the health system. The Ebola outbreak and severe acute respiratory syndrome corona virus-2 (SARS-CoV2) in the recent past have also raised the need for better public health management systems and drugs that could effectively treat the infected and vaccines for prophylaxis. The discovery of drugs is a boon to mankind. In present times the use of software's for designing new drugs and repurposing already available (which happen to be more than two billion) has made it possible to be done within time frames. The novel as well existing compounds are pitted against specific target proteins. This is done by evaluation of the protein-ligand affinity thermodynamics using different model systems.[1] This helps in avoiding far end research with inappropriate compounds as the chances of desired results with such compounds is very low. However, a particular compound which does not yield good result against one protein may be a better drug for another target protein. The free energy, enthalpy and binding energies are taken into consideration for selection of the best fit compound for a target protein. Further the ADMET properties of a compound help in screening only those molecules which will have tolerable adverse effects upon administration. This helps in decreasing the cost of drug designing also helps in speeding the transfer of a drug from bench to target population.[2-4] The need and usefulness of such methods has been evident many times. The Ebola virus outbreak could be curbed because of success achieved in

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treating patients with ebola virus by administrating Remdesvir. Such a success could not be achieved for SARS-CoV2 so far. Only a few drugs including Remdesvir, hydroxychloroquine.[5-6] The importance of Vitamin D in limiting the fatality in SARS-CoV2 infected patients has been remarkable. It has already been shown that the patients of Caucasian race showed better survival than those the African origin. Studies are already in progression to find the efficacy of Vit. D administration for prophylaxis and treatment.[7-13] The present study is thus an attempt to find the binding affinity of a three commonly used vitamins i.e., vitamins A, D and E to the spike receptor binding domain (SRBD) of SARs-Cov2.

The effect of Vitamin D and A has been highlighted by previous study.[14-16] It acts on the expression of many genes through Vitamin D receptor. The complex of active vitamin D, VDRE retinoid x receptor and 9 cis retinoic acid interacts with vitamin D response elements and Vit D receptor genes. Further vitamins D and A interacts and modulates the functions of respiratory tract mucous membrane a site that is exposed to pathogens. Vitamin D controls the immune system by controlling the functions of WBCs and associated components. Of further importance is cathelicidin, a product of vitamin D stimulation which is antimicrobial in function.[17-19]

METHODOLOGY

The spike protein receptor binding domain without ace2 (Figure 1 (a) PDB id 6moj) was used as a target protein whereas the vitamins A and D were the ligands. The protein structures were downloaded from Protein Data Bank (PDB) and ligands were downloaded from pubchem database (Table 1) in PDB format. The files were uploaded to the web server DOCKTHOR. The protein and ligand were prepared and docked followed by analysis of the generated model systems. The results were downloaded.

RESULTS AND DISCUSSION

There are no highly efficient drugs or vaccines available as of now for COVID-19 treatment and prophylaxis. We have to rely on repurposing of existing antiviral drugs available for treatment of several viral diseases with combination of vitamins (Vit.). In the present theoretical study we tried to find out the best fit ligand by doing insilico analysis. Vitamins, A E and D showed docking scores of -8.274, -8.350 and -7.452 respectively (Table 2). The total energy of the It has been shown in previous work that Vit. E did not show any significant effect in reducing respiratory tract infections, nor it shows any promising effects on reducing the severity of such infections. Instead of reducing it increase morbidity related to respiratory tract infections (RTI) further, Vit. E may compromise the efficacy of Vit. D and Vit. A based immune responses. In our present study we have found the binding energy and total energy of vit E with spike protein is higher (Table) than the binding energy of Vit. D and Vit. A. Hence more studies required to evaluate further the response of Vit E administration on covid patients either in combination with other vitamins or with drugs available for RTI. Our findings are similar to the findings of Masoudi *et al.* (2020)[19] using MOE 2105 and Autodock vina for the affinity of vitamin D to 3CLpro an RNA dependent RNA polymerase.

CONCLUSION

We have found three vitamins which showed H- bond interactions with spiked without ACE2 receptor. The Vitamins A and D which also form complex that modulates the immune system are of importance. The administration of vitamin D in combination with vitamin A is an important aspect which needs to be explored further for usefulness in prophylaxis and improving the chances of recovery in Covid 19 patients.

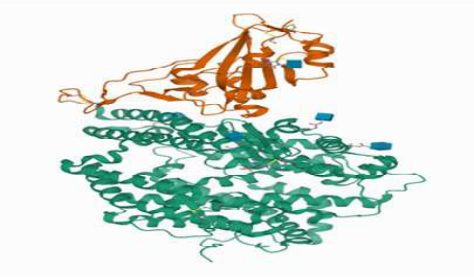


Figure a. The crystal structure of SARS-COV2-Receptor binding domain of spike protein (PDB code -6MOJ)

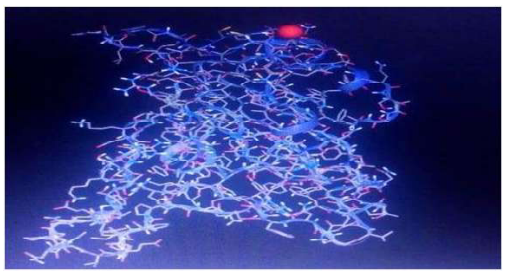


Figure b. SARS-COV2-Receptorbinding domain of spike protein after preparation on Dockthor webserver.

Table 1. Shows the Ligands and their 2D structures

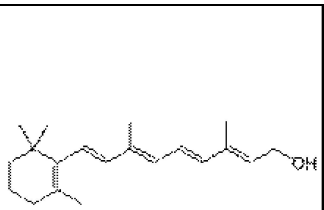
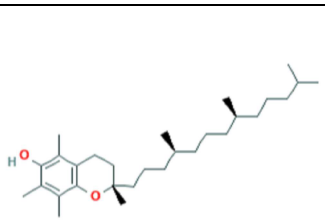
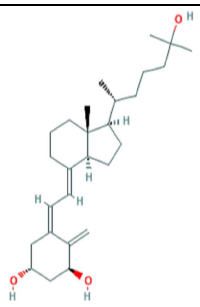
Sl. No.	Chemical structure			
1	Name	Retinol	Tocopherol	Calcitriol
2	Souce/Id	PubChem CID: 445354	PubChem CID: 14985	PubChemCID: 5280453

Table 2. Shows the binding affinity and total energy for the docking to the Spike receptor binding domain without ACE2.

Sl. No.	Ligands	Score	Total Energy	Vander Waal's	DockThor Job-id
1	Retinol	-8.274	98.72	-15.634	spikeminusaceretin_5f95238334442
2	Tocopherol	-8.350	303.323	-14.365	spikeminusacetcho_5f9511dcd6602
3	Calcitriol	-7.452	93.619	-14.621	spikeminusacecalcitriol_5f9504194ee3c

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