Computational approach revealed potential affinity of antiasthmatics against receptor binding domain of 2019n-Cov spike glycoprotein

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Abstract

The novel COVID-19 pandemic is now a health threat, with a deep-felt impact worldwide. The new coronavirus 2019 (2019 n-Cov) binds to host human receptors through Receptor Binding Domain RBD of Spike glycoprotein (S), making it a prominent drug target. The present study aims to identify new potential hits that can inhibit the S protein using in silico approaches. Several natural and synthetics compounds (antiasthmatics, Antiviral, Antimalarial, Antibacterial, Anti-Inflammatory, cyclic peptide, and cyclic bis) were screened by molecular docking using AutoDock Vina. Additionally, we tested calcitriol and three known drugs (Azithromycin, HydroxyChloroquine, and Chloroquine) against the spike protein to found if they have any direct interaction.

Our finding consists of 4 potential synthetic compounds from PubChem database, known for their antiasthmatic effects, that show highly binding energies each (-8.6 kcal/mol, 7.7kcal/mol, -7.2 kcal/mol and -7.0 kcal/mol). Another 5 natural compounds from the South African natural sources database (SANCDB) that bind to RBD of Spike with significant energy each: (Marchantin C with -7.3 kcal/mol, Riccardin C with -7.0 kcal/mol, Digitoxigenin-glucoside with -6.9 kcal/mol, D-Friedoolean-14-en-oic acid with -6.8 kcal/mol and, Spongotine A with -6.7 kcal/mol). The FaF-Drugs server was used to evaluate the drug-like properties of the identified compounds. Additionally, Calcitriol, Azithromycin, and HydroxyChloroquine have an appreciable binding affinity to 2019-nCoV S, suggesting a possible mechanism of action. Using in silico approaches like molecular docking and pharmacokinetic properties, we showed new potential inhibitors. Our findings need further analysis, and chemical design for more effective derivatives of these compounds speculated to disrupt the viral recognition of host receptors.

Keywords: Covid-19 Spike, antiasthmatics, natural compounds, molecular docking, prediction, treatment.

Introduction

The novel coronavirus (2019-ncov) has spread rapidly since its recent identification in patients with severe pneumonia in Wuhan, China. Today, the outbreak causes a public health emergency of international concern. According to the World Health Organization (WHO), as of 27 March 2020, the number of COVID-19 cases surpassed 550,000 globally, leading to more than 25 000 deaths.

Up to date, no vaccine approved to treat human coronaviruses but, recently, cell culture studies and clinical trials have suggested hydroxy-chloroquine, an anti-malarial drug and antibiotic azithromycin as a treatment of covid-19[1],[2] Simultaneously, several studies did focus on repurposing existing antiviral agents, some of which are already moving into clinical trials[3]. The 2019-nCoV infection, now named COVID-19, causes a severe respiratory illness similar to severe acute respiratory syndrome coronavirus (SARS) [4].

Phylogenetic and genomic characterization showed that the 2019-nCoV fell within the genus Betacoronavirus and is sufficiently divergent from SARS-CoV (with 88% identity) to be considered a new betacoronavirus and might bats represent an intermediate host facilitating the emergence of the virus in humans[5] .

Coronaviruses recognize human angiotensin-converting enzyme 2 (ACE2) receptor through their spike glycoprotein (S), which makes an entry into human cells, It is a trimeric class I which consists of S1 and S2 subunits. S1 Subunit binds to a receptor on the host cell surface and then through its S2 subunit fuses viral and host membranes , There are two different conformations of the spike protein, the metastable prefusion and the stable postfusion. The transition from prefusion to postfusion conformation leads to membrane fusion, while the S1 subunit of the receptor-binding domain (RBD) binds to a host cell receptor, this process destabilizes the trimer prefusion structure, which results in a loss of S1 subunit, and, a transition from the S2 subunit to a stable postfusion conformation [6]. The spike glycoprotein is a potential target for treatments and diagnostic. This month the cryo-electron microscopy structure of the 2019-nCoV S trimer in the prefusion conformation was determined by Wrapp et al [7]. The atomic-level detail of the new structure of spike in the prefusion conformation will lead to more prominent screening with the design of small molecules for potential inhibition. In this study, we used molecular docking to screen multiple compounds from south Africa natural compounds database (SANCDB) and, PubChem database against RBD of spike glycoprotein to identify potential hits, that can inhibit the RBD of the spike protein. Additionally, we tested Calcitriol and three known drugs (Azithromycin, Hydroxy-Chloroquine, and Chloroquine) to study their binding affinity to RBD spike 2019 n-Cov.

Methods

Protein Preparation

The Cryo-EM structure of the 2019-nCoV spike in the prefusion (PDB ID: 6VSB) was retrieved from Protein Data Bank (https://www.rcsb.org/structure/6VSB . We used Swiss model web-server [8] to model the missing residues, then the structure was prepared for the docking through Mgltools 1.5.6 of AutodockTools [9].

Ligand preparation

Chemical structures of Antiasthmatics compounds were taken from PubChem and Antiviral, Antibacterial , Antimalarial, anti-inflammatory, cyclic peptide, cyclic and acyclic bis were taken from South Africa Natural Compounds Database (SANCDB)[10]. The optimisation of all compounds structures was done by adding partial charges and setting torsion angles in Mgltools 1.5.6 of AutodockTools.

Molecular docking

We performed Docking with the AutoDock Vina program (Trott et Olson 2010). The grid was defined to enclose the interface RBD/host receptor with a size of 92 ×48 ×42 along x, y, and z-axis and, hit compounds were selected based on the lowest binding affinity and Root-Mean-Square Deviation (RMSD) value.

Ligand receptor interaction analysis

For a clear view of receptor-ligand interaction of the best-docked complexes, we analyzed the 2D plots of receptor-ligand interactions using the Ligplot+ tool [11]. It generates a 2D graph of hydrogen bonding and hydrophobic interactions which, contribute to the affinity of compounds within the RBD of Spike.

Drug-Like Properties of the Identified hits

Computational approximation of the absorption, distribution, metabolism, excretion, and toxicity (ADME tox) of identified hits were predicted virtually. Also, to eliminate Pan Assay Interference Compounds(PAINS), the substructure that appears as frequent hitters (promiscuous compounds) in many biochemical high throughput screens [12] such as Quinones-like or Rhodanines-like the structures that are widely reported to be false positives, We used FAF-Drugs3 filtering [13].

Possibility of interaction of four Known drugs with RBD of Spike are Studied Based on literature, we tested Chloroquine, Hydroxychloroquine, Azithromycin, and Calcitriol by molecular docking

to study their binding affinity to the RBD spike of the 2019 n-Cov. The 3D structures were obtained from PubChem except for Azithromycin, which was from PDB. The reparation and docking of these structures were done by Autodock vina.

Results

Identification of Hits from PubChem and SANCDB

Docking studies were performed to identify the compounds that bind to the binding site of the S protein. A total of 101 compounds from the SANCDB and PubChem databases, were subjected to molecular docking approaches, which led to the identification of 3 antiasthmatics and 5 natural compounds (Table 1) (Figure 1.2.3) exhibiting inhibitory potential. We selected eight identified hits for drug-like filtering.

Databases	Compound Name and Identifier	Classification or use	Chemical formula	Binding Affinity (Kcal/mol)	Residues interaction with Ligand Through hydrogen bonding	Hydrophobic binding
PubChem	CID 11855358	Antiasthmatics	$C_{21}H_{12}F_7N_3O_4$	-8.6	Leu492, Tyr489, Gly485	Gln484, Pro491, Lys462, **Leu455**, Phe456, Lys417,
PubChem	Setileuton (CID11856170)	Antiasthmatics	$C_{22}H_{17}F_4N_3O_4$	-7. 2	Tyr489, Gly485, Gly484	Lys462 , **Gln493** , Pro491, Asn487, Glu484, Leu492
PubChem	(CID11855629)	Antiasthmatics	$C_{23}H_{20}FN_3O_4$	-7 .7	**Gln493**, Leu492, Glu484	Pro491, **Leu455**, Lys417, Phe456, Leu461, Lys462, Tyr489, Phe490 , Gly485
SANCDB	Marchantin C (SANC00768)	Cyclic bis	$C_{28}H_{24}O_4$	-7.3	**Gln493**	Leu492, **Leu455**, Pro491, Gln484, Val483, Asn481, Gly482, Asn487, Gly485, Tyr489
SANCDB	Riccardin C (SANC00770)	Cyclic bis	$C_{28}H_{24}O_4$	-7.00	Arg454, Arg 457	Cys488, Phe486, Tyr489, Phe490, Gln474, Ala475, Gly476
SANCDB	Marchantin H (SANC00772)	Cyclic bis	$C_{28}H_{24}O_5$	-7.7	**Gln493**	Leu492, **Leu455** , Pro491 , Glu484 , Val483 , Gly482 , Asn487 , Tyr489 , Gly485
SANCDB	Parviflorone F(SANC00369)	Antimalarial	$C_{27}H_{30}O_6$	-6.9	Tyr489, Gly485	**Gln493**, Leu492 , Pro491, Gln484 , Leu452, Asn450, Tyr449 , Ser494
SANCDB	Digitoxigenin-glucoside (SANC00279)	Antiviral	C29H44O9	-6.9	L492, Glu484, Gly482	**Gln493**, **Leu455**, Phe456,Lys417, Lys462, Pro491, Tyr489, Val483

Table 1: Summary of top eight ranked hits screened against RBD of Spike 2019 n-cov, with their respective classification, Chemical formula, binding affinity, hydrogen and hydrophobic interacting residues.

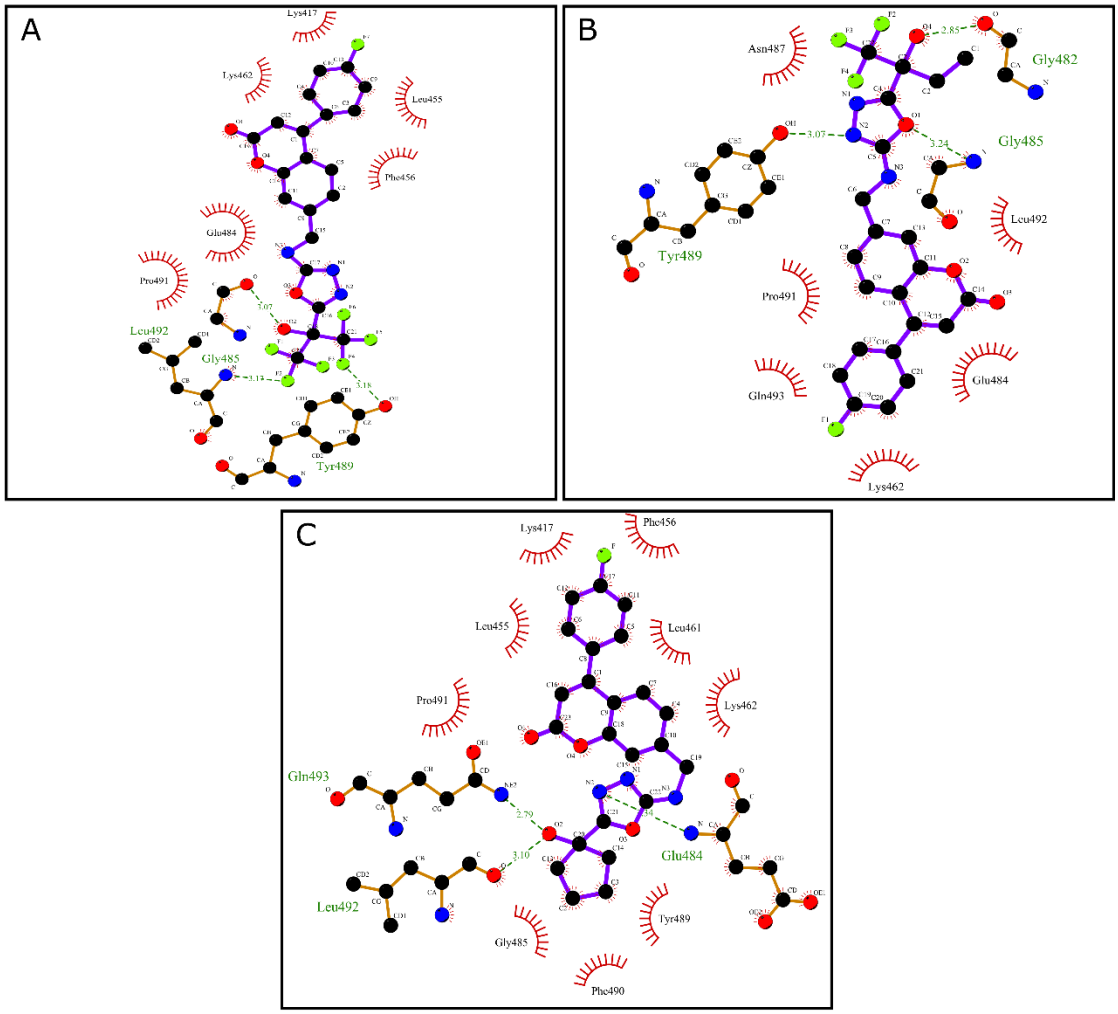

Figure 1: LigPlot+ analyses results of binding conformation of three potential hits from PubChem (A= CID11855358, B= Setileuton, C= CID11855629).

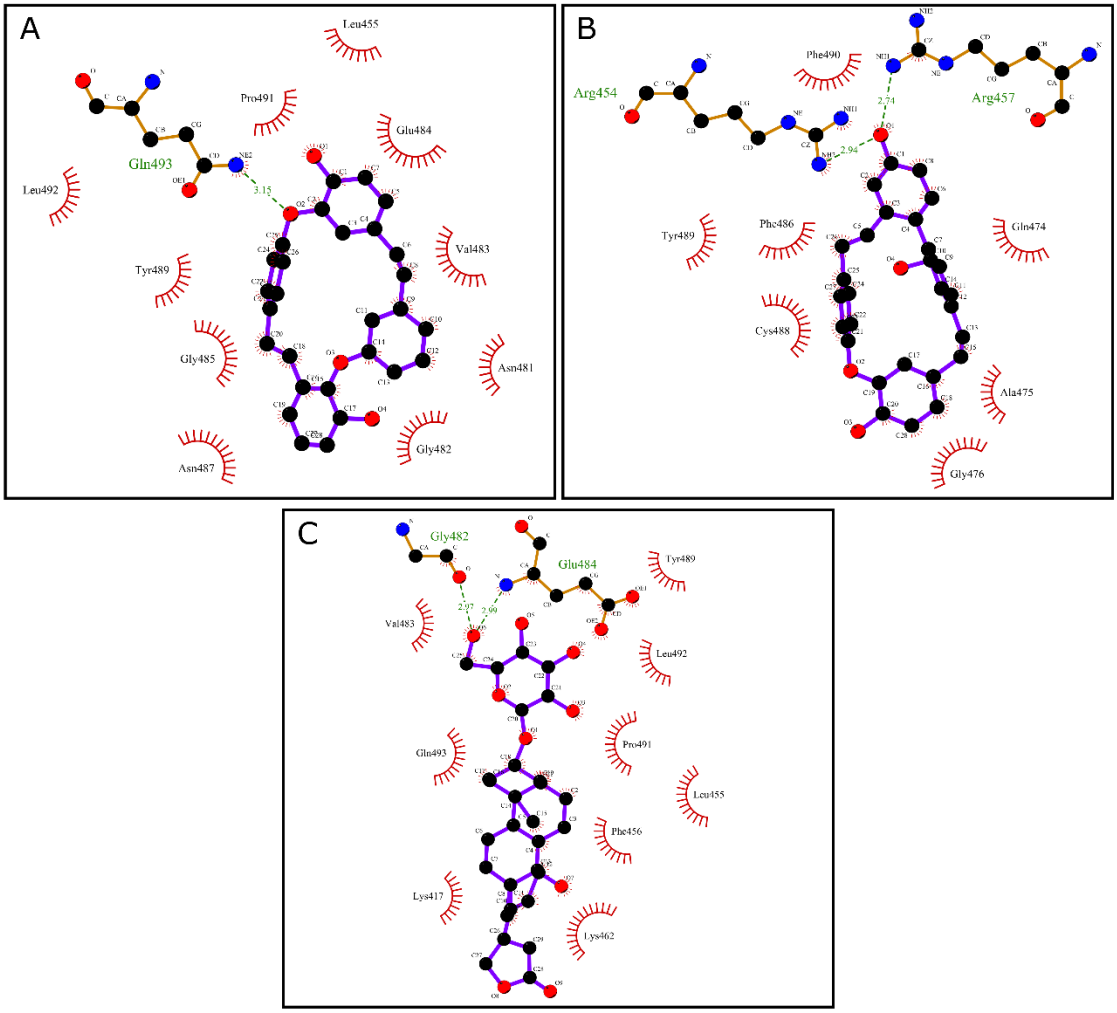

Figure 2: LigPlot+ analyses results of binding mode of natural hits (A= SANC00768, B= SANC00770, C= SANC00279) with RBD spike 2019n-cov.

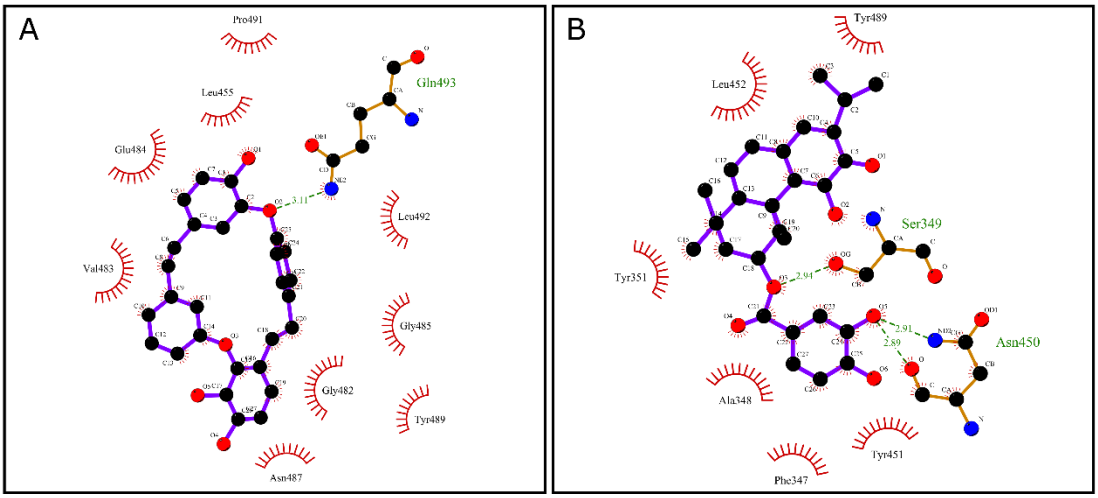

Figure 3: LigPlot+ analyses results of binding conformation of (A= SANC00772 , B= SANC00369) with RBD spike 2019n-cov.

Drug-Like Properties of the Identified Hits

To evaluate the pharmacokinetic properties of the identified hits, we tested the drug-likeness based on Lipinski's rule of five (Ro5) and Pan Assay Interference Compounds filter to recognize the presence of the chemical groups that belong to the PAINS category (Table 2).

Six out of eight hits have been accepted as drug-like and passed the physicochemical filter with no structural alerts. The 2 discarded hits, SANC00772 and SANC00369, had the quinone group in the PAINS sub-structural moieties.

Compounds name and/or ID	FAF-Drugs3 filtering	PAINS filtering
(CID 11855358)	Accepted	None
Setileuton (CID11856170)	Accepted	None
(CID11855629)	Accepted	None
Marchantin C (SANC00768)	Accepted	None
SANC00770	Accepted	None
SANC00772	Intermediate	catechol
SANC00369	Intermediate	catechol
SANC00279	Accepted	None

Table 2: FAF-Drugs3 and pan assay interference (PAINS) filtering of 8 identified hits from PubChem and SANCDB database.

Binding of known drugs and calcitriol with RBD Spike of 2019n-cov

Calcitriol and three known drugs were docked against the RBD of Spike glycoprotein and, top-ranking docking poses were selected based on the top lowest energy of binding and RMSD equals of zero for a reproduction of the correct pose, Calcitriol and three drugs including Azithromycin, hydroxy-chloroquine, and chloroquine (Table 3) were observed to bind with appreciable binding affinity within the active site of the RBD S proteins (Figure 4). Calcitriol with a binding energy of −5.5Kcal/mol forming hydrogen bonds with Gln493, while other hydrophobic interacting residues were Ser494, Tyr449, Asn450, Leu452, Tyr489, Leu492, Glu484 (Fig 4.A). Azithromycin interacts with a binding energy of −5.3Kcal/mol form one hydrogen bond and hydrophobic interaction with 7 residues of the RBD (Fig. 4.B). Hydroxy-chloroquine (Fig.4.C) showed also acceptable binding energy with RBD active site residues including three hydrogen bonds and hydrophobic interaction with ten residues (Tyr449, Leu452, Ser494, Leu492, Gln493, Glu484, Phe490, Glu484, Pro491), followed by Chloroquine whose binding energy was lower(Fig.4.D).

Database	**DRUGS Name and ID**	**Binding Affinity (kcal /mol)**	**h-bonds interaction**	**Hydrophobic interaction**
PubChem	Calcitriol (CID528073)	-5.5	**Gln493**	Ser494 , Tyr449, Asn450, Leu452, Tyr489, Leu492 , Glu484
PDB	Azithromycin 1M1K (CID447043)	-5.3	Tyr449	Asn450, Tyr451, Ser349, Ala348, Phe347, Tyr351, Arg346
PubChem	Hydroxychloroquine (CID3652)	-5.2	Tyr489, Asn487, Gly485	Tyr449, Leu452, Ser494, Leu492, **Gln493**, Glu484, Phe490, Glu484, Pro491
PubChem	Chloroquine	-4.5	Arg454	Cys488, Phe486, Cys488, Tyr489, Arg457, Lys458, Gln474, Gly476

Table 3: Results of top ranked pose of calcitriol and knowns drugs docked against RBD of Spike 2019 n-cov, with their respective binding affinity, hydrogen and hydrophobic interacting residues.

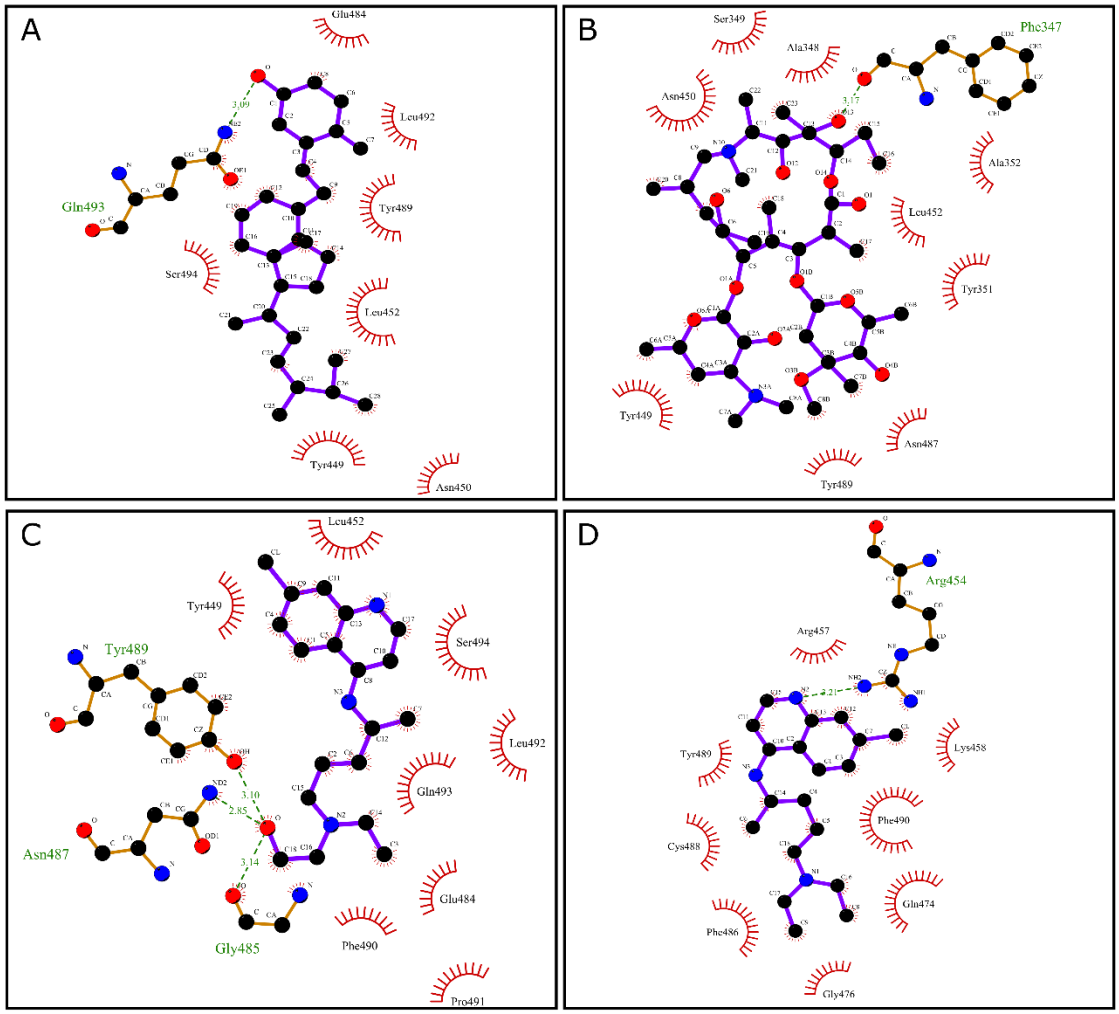

Figure 4: LigPlot+ analyses results of binding conformation of (A= Calcitriol , B= Azythromicin, C=HydroxChloroquine, D=Chloroquine) with RBD spike 2019n-cov.

Discussion

Molecular docking has become an increasingly powerful tool for drug discovery. it is used to model the binding between proteins and small molecules at the atomic level, which allows us to characterize the behavior of small molecules in the binding site of target proteins[14]. The process of docking consists of predicting the conformation of the ligand, it's pose and orientation within these sites, and assessing the energy of binding. In this work using Molecular docking against RBD of spike glycoprotein (PDB ID: 5vsb), About 101 compounds from SANCDB and PubChem databases were screened. We revealed 3 hits from PubChem and 5 other hits from the SANCDB (Table 1) exhibiting inhibitory potential.

The selected analogs from PubChem: CID 11855358, CID11856170, CID11855629 showed the highest energy of binding affinity, respectively: -8.6 Kcal/mol,-7.2Kcal/mol, -7.7Kcal/mol (Table 1). The three potent compounds contain the "1, 3, 4-oxadiazole", which is an essential heterocyclic, with numerous exceptional chemical and biological properties. Its analogs are known to treat various conditions, such as Alzheimer's disease, pain, anticonvulsants, asthma, and postsurgical dermal scarring. Setileuton (CID11856170), known as a particular inhibitor of the 5-lipoxygenase enzyme with potential therapeutic efficacy for the treatment of inflammatory disorders, is under investigation for the treatment of respiratory diseases and atherosclerosis[15] . Furthermore, Setileuton derivatives showed antimicrobial and antifungal properties [16], [17]. We conclude that the three hits identified from the PubChem database have the majority of the necessary pharmacophoric features for an acceptable inhibition of the S protein, including the presence of the electronegative of fluorine (F) group. Moreover, their binding with RBD forms a stable complex with a robust network of hydrogen, hydrophobic bonds (Figure 1) and important residues, namely: Gly485, Leu455, Leu992, Gln493, Gln484, Asn487, and Gln493 which were previously predicted in as residue of direct interaction with the human cell host receptor [18],[19].

The 5 hits identified from a natural source revealed highly binding affinity as well as an appreciable network of interaction (Figure 1.2), include 3 hits belong cyclic bis class SANC00768, SANC00770, and SANC00772 also SANC00369 known with his Antiplasmodial activities [20]. SANC00279 reported to have anti-VIH activity [21]. All the identified hits (5 from natural source and 3 hits from PubChem) were evaluated for pharmacokinetic properties using the ADME tox filtering and the presence of substructure associated with promiscuous binding on protein targets was tested using the pan assay interference compounds (PAINS). As presented in Table 2, all the selected hits has been accepted as drug-like. However, only SANC00772, SANC00369 were

predicted as intermediate because of the PAINS quinone moiety (Figure 3). Despite the PAINS metric is a common tool in virtual screening, up to 5% of the current number of FDA (Food and Drug Administration) drugs have been found to contain PAINS-recognized features[22] ,[23].

Chloroquine is a 9-aminoquinoline used as an antimalarial, and its hydroxy-analog is used in the treatment of autoimmune diseases such as rheumatoid arthritis due to its immunomodulatory properties, which imply a possible use in viral infections. Moreover, in vitro studies revealed their efficiency in inhibiting SARS-CoV-2[5], through changing the glycosylation of ACE2 receptor and spike protein During the viral entry into host cells via endocytosis, the spike protein must be cleaved by endosomal proteases, which are activated upon acidification of the endosome. This cleavage induces the fusion by a conformational change in the spike protein. Thus, chloroquine is likely to alter this fusion by the inhibition of endosomal acidification, so blocking the virus in endosomes [24], [25] .

Molecular docking showed also an acceptable binding affinity with the two new repurposed drugs, which indicates their binding to the RBD of Spike protein (Figure 4.C.D) . Opposed to chloroquine, which binds with (-4.5Kcal/mol) and less interaction stability, hydroxy-chloroquine has elevated binding energy(- 5.2Kcal/mol) with a strong network of hydrogen plus hydrophobic bonds that hold essential residues in the binding site of human cell host. According to the clinical trial, which revealed that Azithromycin reinforce the outcome of hydroxy-chloroquine in the treatment of COVID-19. In our molecular docking analysis, we revealed a possible binding of this macrolide antibiotic into the S protein. Our result hints at a probable and direct effect of hydroxychloroquine and Azithromycin against the 2019n-cov Spike.

Vitamin D is taken either by exposing the skin to the sun, from food or through supplements (vitamin D 3 or vitamin D 2). its main circulating formula is the 25-hydroxyvitamin D [25 (OH) D] and its active formula is the 1, 25-dihydroxy vitamin D [1,25 (OH) 2 D], also known as calcitriol, previous investigations proved the importance of vitamin D in host response via various immune mechanisms, Hence, The vitamin D receptor (VDR) is throughout expressed in epithelial and immune system cells [26], Vitamin D stimulates immune cells in respiratory tracts like macrophages, neutrophils, NK and, epithelial cells to produce antimicrobial peptides (AMPs), such as defensins and cathelicidins [27]. This also inhibits the production of pro-inflammatory cytokines). T cells in VDR knockout mice produce more pro-inflammatory cytokines[28], the

regulation of pro-inflammatory response is beneficial to the host, endangered to respiratory viruses [28], view of the pathogenicity of viruses respiratory is associated with hypercytokinemia, which is potentially lethal inflammatory responses. We used molecular docking to reveal if there any direct interaction with vitamin D itself and S protein of 2019 n-cov , the result showed acceptable binding of hydroxyl groups of calcitriol with three residues of RBD S protein through hydrogen bonds and five residues involved in hydrophobic interactions with (Figure 4.A).

Conclusion

In this study, we revealed six potential inhibitors of RBD of the spike in the prefusion conformation. Antiasthmatics showed the highest potential affinity and could provide a promising treatment of COVID-19. Besides, this class of compounds is already known by their potential therapeutic utility for the treatment of the inflammatory disorder and respiratory disease, which could be interesting in the case of COVID 19. Also, natural compounds revealed appreciable affinity against RBD of spike 2019n-Cov and could provide potential templates for the development of future drugs. Additional we revealed a possible binding between Vitamin D, Azithromycin, and Hydroxy-Chloroquine suggesting direct mechanisms of action.

Conflict of interest

Authors declare that they have no conflict of interest.

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Data Availability

All docking structures are available.

Reference

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