Interaction of SARS-CoV-2 spike protein with angiotensin converting enzyme inhibitors and selected compounds from the chemical entities of biological interest

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Abstract
Background: Recent COVID-19 outbreak has prompted the search of novel therapeutic agents to treat the disease. The initial step of the infection involves the binding of the virus through the viral spike protein with the host angiotensin converting enzyme 2 (ACE2). In this study, the interaction of some ACE or ACE2 inhibitors and their analogues as well as selected compounds with the viral spike protein as a strategy to hinder viral-ACE2 interaction were investigated. SARS-CoV-2 spike protein as well as the ligands were retrieved from protein databank and ChEBI database respectively. The molecules were prepared before initiating the virtual screening using PyRx software. Discovery studio was used to further visualize the binding interactions between the compounds and the protein.

Results: The ACE inhibitors and their analogues fosinopril (-), fosinopril and moexipril have the best binding affinity to the protein with binding energies $<-7.0 \text{ kcal/mol}$ while non-flavonoid stilben-4-ol binds with free binding energy of $-7.1 \text{ kcal/mol}$. Others compounds which belong to either the flavonoids, terpenes and alkaloid classes also have binding energies $<-7.0 \text{ kcal/mol}$. Such high binding energies were enhanced via hydrogen bond (h-bond) interactions in addition to other interactions observed between the compounds and the amino acid residues of the protein.

Conclusions: The ACE inhibitors and their analogues as well as the selected compounds could serve as inhibitors of the spike protein as well as lead in drug discovery processes to target the SARS-CoV-2 virus.

Keywords: SARS-CoV-2, Spike protein, Angiotensin converting enzyme, Flavonoids

1 Background
Coronaviruses (CoV) are large family of zoonotic viruses known to cause illnesses ranging from a common cold to more severe conditions such as respiratory syndrome [1]. The recent outbreak of a novel CoV virus [SARS-CoV-2] disease which originated from Wuhan, China and progressively spread to all parts of the world prompted the World Health Organization (WHO) to declare the disease as a pandemic, named COVID-19 [2]. The virus affects the respiratory system and causes breathing difficulties with chronic pneumonia, severe respiratory syndromes in addition to fever and kidney failure which may lead to death of the patients [3]. Currently, there are no specific known drugs against the disease and the global attention focused on the scientific community for a possible solution.

The observed symptoms of COVID-19 occur as a result of the binding interaction between the virus spike protein and the host Angiotensin Converting Enzyme 2 (ACE2) receptors [4] located on the alveolar cells surfaces in the lungs [5]. This process facilitated the entry of the virus into the infected host cell and therefore, blocking the SARS-CoV-2 S protein could ultimately prevent
the viral-ACE2 interaction and renders the virus non-
infectious. Interestingly, the crystal structure of the spike
protein has been elucidated and released [6]. The trim-
eric protein contains S1 and S2 subunits in addition to
receptor binding domain that altogether play a role in
the binding interaction. Such a fascinating scientific effort is
an important milestone in the search for drugs or vac-
cines against the disease [7]. This is because the spike
protein has been considered to be the most appealing
drug and/or vaccine target by scientists. Moreover, the
current search for COVID-19 chemotherapeutics relied
on drug repurposing and/or repositioning [8]. In these
regards, a number of databases are available for such
purposes and among them, the Chemical Entities of Bio-
logical Interest (ChEBI) is one of the most versatile [9]. It
consists of freely available molecular entities focused on
small chemical compounds as part of Open Biomedical
Ontologies effort which is a resource of the US National
Center for Biomedical Ontology.

As earlier noted, the important role of the ACE2 in
mediating the viral entry into the host cells could sug-
gest that ACE or ACE 2 inhibitors and their analogues
in addition to similar compounds from the ChEBI data-
bases could be explored for drug repurposing research
against the viral spike protein. Additionally, scientific
investigations have showed natural products, especially
flavonoid and non-flavonoid phenolics, terpenes and
alkaloids as promising therapeutic candidates against
the SARS-CoV-2 which might be explored as possible
inhibitors of the viral spike protein [10, 11]. In this study,
we investigated the binding and interaction of ACE or
ACE2 inhibitors and their analogues as well as, flavo-
noids, non-flavonoid phenolics, terpenes and alkaloids
available in ChEBI with the SARS-CoV-2 spike protein
using molecular docking. The result obtained could add
to the wealth of information for the ongoing search of
lead compounds against COVID-19 by the scientific
community.

2 Methods
2.1 Retrieval and preparation of SARS-CoV-2 spike protein
The Cryo-EM structure of the trimetric SARS-
CoV-2 spike protein containing N-acetyl-D-glucosamine
(PDB ID: 6vsb) was extracted from RCSB Protein Data
Bank (http://www.rcsb.org). The protein was prepared for
molecular docking using Chimera docking software ver-

tion 1.14 (https://www.cgl.ucsf.edu/chimera/download.
html). In the Chimera, chains B and C in addition to the
NAG contained in the protein structure were removed.
Subsequently, the remaining chain A was docked prep
by adding h-bonds while all other settings were set
as default. After preparation, the chain A of SARS-
CoV-2 spike protein was saved in a PDB format and
transferred to PyRx virtual screening software (https://
pyrx.sourceforge.io/). Therein, the molecule was pre-
pared as autodock molecule and stored in pdbqt format.

2.2 Retrieval and preparation of ligands 3-D structures
All the ligands used for the docking experiment were
retrieved from ChEBI database. Additionally, the 3D
structures of twenty seven (27) ACE inhibitors, 2 ACE2
inhibitors and their structural analogues were retrieved
from the database. Moreover, nineteen (19) non-fla-
vonoid phenolics, twenty three (23) flavonoids, twelve
(12) terpenes and ten (10) alkaloids were also retrieved
from the database for the subsequent docking experiment.
The compounds were retrieved as SDF files and were
imported to the PyRx virtual screening software (https://
pyrx.sourceforge.io/). Following retrieval, ligands were
prepared by applying universal force field (UFF) to mini-
mize all the minimum energy for each configuration.
Thereafter, the ligands were converted to the pdbqt for-
mat (autodock ligands) in preparation for docking.

2.3 Molecular docking
For the molecular docking experiment, the autodock
ligands were docked against the SARS-CoV-2 spike pro-
tein. This was initiated by commanding the Vina wizard
to commence the docking process followed by maximiz-
ing (in the absence of ligand) the Auto Grid boxes center
\((x, y, z)\) coordinates \((206.048, 223.411, 226.7943)\) and
dimension \((x, y, z)\) coordinates \((82.8917, 79.9188, 168.0678)\)
to cover the entire protein and accommodate ligand to
move freely and select the best binding site. In the PyRx
software, the binding energies of the interactions which
indicate the best predicted binding modes to the proteins
[12, 13] were computed and retrieved in Microsoft excel.

2.4 Structural analysis and visualization
To further visualize the docking result and deduce the
possible receptor- ligand interaction, Discovery studio
visualizer (https://www.3dsbiovia.com/products/colla-
borative-science/biovia-discoverystudio/visualization-
download.php) was used for the obtained docking results
contained in the working directorate. The 2-D interac-
tions were visualized in order to determine possible bond
interactions between amino acid residues of the SARS-
CoV-2 spike protein and the ligands. Bond lengths were
also calculated using the software.

3 Results
Docking of ACE-2 inhibitors and analogues against the
SARS-CoV-2 spike protein showed fosinopril (1-), fos-
inopril, moexipril and novacine to have the best affinity
to the protein with free binding energies \(\geq 7.0\) kcal/

mol (Table 1) while stilben-4-ol had the best binding
Table 1  Binding energies (B/E) of compounds against SARS-CoV-2 spike protein

| ACE/ACE 2 inhibitors/derivatives | B/E (Kcal/mol) | Non-flavonoid Phenolics B/E (Kcal/mol) | Flavonoids B/E (Kcal/mol) | Terpenes B/E (Kcal/mol) | Alkaloids B/E (Kcal/mol) |
|----------------------------------|----------------|----------------------------------------|---------------------------|-------------------------|--------------------------|
| Captopril                        | −5.3           | 2-methoxy-6-(all trans-nonaprenyl)phenol | −5.5                      | Quercetin               | −6.7                     | Rediocide A              | −8.0                     | Mesulergine              | −7.5                     |
| Captopril disulphide             | −5.7           | 2-polyaprenylphenol                     | −6.1                      | Cudraflavone            | −7                       | α-pinene                 | −5.1                     | Daphane                  | −6.2                     |
| 3-acetyltio-isobutyric acid       | −4.5           | 3,5-dimethyl-4-(methyl)Sulfanylphenol    | −5.2                      | Artocarpin              | −7.2                     | β-pinene                 | −6.1                     | 3-pyridyl-lactic acid    | −5.6                     |
| Benazepril                       | −5.3           | 4-methylaminophenol                     | −5.1                      | Papyriflavonol          | −7.2                     | Nerol                    | −4.1                     | Precondylocarpine acetate | −6.9                     |
| Benazepril (1+)                  | −6.8           | Thymol                                  | −5.9                      | 7-hydroxyflavone        | −7.2                     | Farnesol                 | −5.4                     | Dihydroprecondylocarpine acetate | −6.3                     |
| Zofenopril                       | −5.8           |                                         |                           |                         |                          |                          |                          |                          |                          |
| Benazepril hydrochloride         | −6.1           | Propofol                                | −5.5                      | Galangin                | −6.8                     | Phytole                  | −5.8                     | 3-aminopentalenol        | −3.4                     |
| Benazeprilat                     | −6.8           | stilben-4-ol                            | −7.1                      | Primetin                | −7.3                     | PhytolaccosideB          | −7.1                     | Dehydrosescodeine        | −5.8                     |
| Enalapril                        | −5.7           | Triclosan                               | −5.6                      | Scutellarein            | −7.6                     | α-ionone                 | −6.0                     | Secodine                 | −6.1                     |
| Enalapril malate                 | −4.7           | Aspergillusene                          | −5.2                      | Tangeratin              | −5.8                     | β-ionone                 | −6.1                     | Lupanine                 | −6.2                     |
| Enalaprilate (anhydrous)         | −6.7           | biphenol F diglycidylether              | −5.7                      | Cirsiliol               | −6.5                     | Dehydrovomfoliol         | −5.2                     | Hapalin-dole             | −7.8                     |
| Enalaprilat dehydrate            | −1.9           | 2-acetylphenol                          | −6                       | Cirsilineol             | −7.5                     | Linalool                 | −4.2                     |                          |                          |
| Fosinopril                       | −7.1           | 2-ethoxyphenol                          | −4.7                      | Nevadensin              | −6.1                     | Geranylacetate           | −4.4                     |                          |                          |
| Fosinopril (1-)                  | −7.2           | mycophenolic acid                       | −6.8                      | Quercetagenitin         | −7                       |                          |                          |                          |                          |
| Fosinoprilat                     | −5.6           | Neotriptophenolide                      | −6.6                      | Robinetin               | −7.7                     |                          |                          |                          |                          |
| Lisinopril                       | −5.4           | 2,3,4,5-tetrachlorophenol               | −5.5                      | Sinensetin              | −6.2                     |                          |                          |                          |                          |
| Lisinopril dehydrate             | −1.9           | 2-acetamidophenolsulfate (1-)           | −5.1                      | Tectochrysin            | −7.5                     |                          |                          |                          |                          |
| Moexipril                        | −7             | 2-acetamidophenolsulfate                | −5.3                      | Frutinone A             | −7.1                     |                          |                          |                          |                          |
| Methyl-1-methyl-5-oxoprolinate   | −4.7           |                                          |                           | Violanthin              | −7.7                     |                          |                          |                          |                          |
| Moexipril hydrochloride          | −6.2           | Triptophenolide methyl ether            | −6.5                      | Wogonin                 | −6.9                     |                          |                          |                          |                          |
affinity among the phenolics with a free binding energy of -7.1 kcal/mol. The flavonoids, cudraflavone, artocarpine, papyriflavonol, 7-hydroxyflavone, primetin, scutellerein, quercetagetin, robinetin, violanthin, isoharmnetin-3-O-rutinoside, cirsilineol, tectochrysin, frutinone A, pelargonidin-3-O-rutinoside betaine and narrrutin had binding energies \( \geq -7.0 \) kcal/mol respectively. Moreover, among the terpenes and alkaloids,
rediocide A, phytolaccoside B, mesulgine and hapalindole have highest binding affinity to the protein than others (Table 1). Among the selected classes of compounds, it was noted generally that the number of flavonoids with good binding affinity to the SARS-CoV-2 spike protein was the highest (Table 1).

Visualization of the receptor-ligand interaction revealed the presence of h-bond interactions which contributed to the observed binding energies realized in the docking (Table 2). Among the ACE inhibitors and their analogues, fosinopril (1-) have two h-bond interactions with His1058 and Gln853 residues of the protein while moexipril and novacine formed a single h-bond with His1058 and Ser591 residues respectively. In the case of fosinopril and the non-flavonoid phenolics stilbene-4-ol, there were absence of h-bond interaction with

![Fig. 1 3-D structure representation of (A) Fosinopril (B) Fosinopril (1-) C Novacine D Stilbene-4-ol E Robinetin F Narirutin G Rediocide A H Phytolaccoside B I Mesulergine J Hapalindole complexed with SARS-CoV-2 spike protein respectively](image)
the protein. Similarly, all the flavonoids formed 1 or more h-bond interactions. Among the flavonoids, quercetin formed 5 h-bonds with Phe342, Asn343, Ser373, Ser375 and Arg509 residues of the protein followed by scutellerein and isoharmetin-3-O-rutinoside with 4 h-bonds each. Nonetheless, the terpenes, rediocide A and phytolaccoside B formed 2 h-bonds interactions with the protein mainly involving Ala713, Tyr1047, Gln564 and Phe565 respectively while the alkaloid, hapalindole formed 1 h-bond interaction with Met731 (Table 2).

In addition to the h-bond, other interactions such as van der Waal interactions, pi-Alkyl interactions, carbon-hydrogen interactions, pi-Sigma interactions among others were found to be critical to the high binding affinities
Fig. 1 continued
of the compounds to the SARS-CoV-2 spike protein (Fig. 1). Noticeably, the ACE inhibitors (fosinopril and fosinopril (1-)) as well as the alkaloid hapalindole formed unfavorable positive-positive interaction with the protein while unfavorable donor-donor interaction was observed with the non-flavonoid stilbene-4-Ol (Fig. 1).

4 Discussion
The increasing number of COVID-19 cases worldwide has become a public health concern that demand an urgent scientific attention [14, 15]. One of the important strategies to prevent the virus from exerting damage to the host is by blocking viral-host interaction which is mediated through the spike protein [16]. In this regard, PyRx software which is a very versatile and powerful tool was used in virtual screening of compounds from ChEBI database against SARS-CoV-2 spike protein without initial validation. This is because the SARS-CoV-2 spike protein was obtained through cryo-EM without any ligand and similar software was used in screening of antiviral compounds as potential inhibitors of SARS-CoV-2 methyltransferase [17]. Although there were a lot of conflicting reports on the use of ACE2 inhibitors on COVID-19 patients [18, 19], our docking results showed fascinating binding interaction between the ACE inhibitors and the spike protein. The presence of phosphinate group in fosinopril and fosinopril (1-) suggests the reason for their observed high binding affinity than the other ACE inhibitors. The group has been reported to specifically bind to ACE and inhibit the production of angiotensin II [20]. The presence of h-bond interaction of fosinopril (1-) with the SARS-CoV-2 spike protein might have further contributed to its high binding affinity. Such interaction occurs at the S2 subunit of the protein since the His1058 and Gln853 residues are found within the region [21]. Similarly, moexipril and novacine formed h-bond interactions at the S2 and S1 subunit of the protein respectively. As the S1 and S2 subunits of the protein enhance receptor binding and viral fusion [22, 23], our result showed the possibility of the inhibitors to be used against the protein [24]. Meanwhile, it is worthy to state that two proline residues were added at the C-terminal fusion machinery of the SARS-CoV-2 spike protein (6VSB) but that was not envisaged to affect the biochemical features of the protein because it was mainly useful during Cryo-EM process.

Natural compounds such as non-flavonoid and flavonoid phenolics, terpenes and alkaloids have gained a lot of attentions as they serve as lead during drug discovery processes [25]. Some of these compounds have been recently exploited as possible inhibitors against SARS-CoV-2 proteins [10, 26]. For the first time, investigation of such compounds against the viral spike protein might further support their efficacy against the virus.

The anti-viral effects of non-flavonoids and flavonoid phenolics have been reported in numerous studies [10, 27]. Most of their anti-viral effects have been known to occur via several mechanisms including the blockage of viral entry which is consistent with our findings [28]. High binding affinities in addition to observed h-bond interaction between the compounds showed their possible efficacy against the SARS-CoV-2 spike protein. Interestingly, most of the compounds interacted with the protein at the S2 sub-unit with the exception of robinetin and violanthin that interacted with the protein’s amino acid residues at S1 sub-unit. Specifically, the reported anti-viral effects of several non-flavonoids and flavonoid phenolics such as quercetin, artocarpin, tectochrysin and stilbene-4-Ol among others, against different human and animal viruses [29, 30] further support our investigations.

Terpenes and alkaloids are another class of compounds reported to possess anti-viral activities. For instance, β-pinene was found to masks herpes virus structure which is necessary for the viral entry into the host [31]. Such mechanism could explain the observed high binding interaction of terpenes with the SARS-CoV-2 spike protein. The presence of benzoic acid in the diterpenoid reidiocide A and the triterpenoid nature of phytolaccoside B could suggest the higher binding interactions with the spike protein. Although there is a scantly information on the antiviral effects of the above mentioned compounds, many reports have proved the anti-influenza activities of benzoic acid derivatives [32] while triterpenoids have been known to exhibit a wide range of effects on respiratory viral infections [33, 34]. The ergoline in addition to sulfuric and o xo-acids structure of mesulergine as well as the indole ring of hapalindole alkaloids give them ability to interact reasonably well with the SARS-CoV-2 spike protein. Most of these compounds interacted with the S2 sub-unit of the protein.

5 Conclusions
Based on our findings, it become paramount that ACE inhibitors and the selected compounds from the ChEBI database could interact reasonably well with the SARS-CoV-2 spike protein. Our data suggest that the compounds could be exploited as anti-COVID-19. Our future work will focus on the experimental validation of some of the findings in order to confirm the conclusions.

Abbreviations
ACE2: Angiotensin converting enzyme 2; ChEBI: Chemical entities of biological interest; COVID-19: Novel coronavirus disease for 2019; NAG: N-Acetyl glucosamine; PDB: Protein database.
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Authors’ contributions
SA performed the in silico studies and Drafted the manuscript; MAJ assisted in analysis of the in silico result and compilation of the manuscript; ABS proof-read the manuscript. All authors have read and approved the manuscript.

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