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ORIGNAL ARTICLE

Simulation of polyketides and phytochemicals as a COVID-19 inhibitor

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Abstract

Severe acute respiratory syndrome coronavirus-2 is a single stranded, non-segmented, positive sense RNA enveloped virus and is responsible for a pandemic Coronavirus disease 2019. It has four structural and non-structural proteins, the spike, envelope, membrane, nucleocapsid protein and some non-structural proteins. The spike protein specifically targets angiotensin converting enzyme receptor 2 (ACE2) in the RBD host cell. Catechins and Epigallocatechin gallate (EGCG) are active phytochemicals and are found in green tea and black tea. Polyketides are phytotoxic fungal secondary metabolites. In silico, two phytochemicals and nineteen polyketides has been simulated by molecular docking for finding potential inhibitor. Asn546, Ser420, Ser545, Asp543, Asn90, Thr92, Lys26, Val93, Asn 322, Met323, Trp326, Asn53, Asn58, Thr55, Glu57, Gln 340, Phe342, Asn343, Gly339 has been found active residues in ACE2. ACRL Toxin II, ACRL Toxin III and ACRL Toxin I, Lovastatin and Biscopyran has showed very promising binding energy (ΔG kcal/mol) among all other selected molecules i.e., ΔG= -7.5117, ΔG= -6.9663, ΔG= -6.3194, ΔG= -6.286, and ΔG= -6.7564 kcal/mol, respectively. Conclusively, these polyketides (ACRL toxins, Lovastatin and Biscopyran) have showed higher inhibiting interaction with ACE2 as compared to tested phytochemicals (Catechins and EGCG). This will guide the researcher to investigate further these chemicals practically on the animals for finding new drugs.

Keywords

SARS-CoV-2
Polyketides
Angiotensin Converting Enzyme Receptor 2
ACRL toxins
Lovastatin
Biscopyran

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Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) appeared in China, December 2019 and has been found responsible for a pandemic Coronavirus disease 2019 (COVID-19). Genome sequencing and phylogenetic analyses showed that it could be present in bat and other wild animals (Zhou et al., 2020). Genetically, it is a positive-sense, single-stranded RNA, and non-segmented virus. It is believed to have zoonotic origins and has close genetic similarity to bat coronaviruses. Taxonomically, it belongs to the main Coronaviridae subfamily-Orthocoronavirinae-is subdivided into alpha (α) (type 1 or phylogroup 1), beta (β) (type 2 or phylogroup 2), delta (δ), and gamma (ϒ) coronavirus genera. Naturally, Alpha-(α) and Beta-(β) CoV belongs to mammal's viruses, whereas Delta-(δ), and Gamma- (ϒ)-CoV belongs to avian viruses (Woo et al., 2012).

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The SARS-CoV-2 has four main structural proteins, the spike (S protein), the envelope, the membrane, the nucleocapsid and some non-structural proteins (Nsp). A glycoprotein known as hemagglutinin esterase exists on the structure of β-strands (Hilgenfeld, 2014). The S Protein comprises the S1 and S2 subunits. Both subunits perform a key role in the COVID-19 pandemic, the S1 subunit binds the SARS-CoV-2 to the host cell with its receptor-binding domain (RBD), while the S2 subunit fuse the membrane to ensure the infection (Du et al., 2009). The S Protein is known to specifically target angiotensin converting enzyme receptor 2 (ACE2). Several studies on the properties of the structural proteins of SARS-CoV-2 support the researchers to identify the main pharmacological targets/marks (Mhatre et al., 2021a). This protein is known to specifically target angiotensin converting enzyme receptor 2 (ACE2) in the RBD host cell. The infection begins with the attachments of spike and RBD of ACE2 receptor, so changes in protein structure can lead to find the target drug for the inhibition of COVID-19 (Mhatre et al., 2021a).

Techniques for diagnostics and maintain the hygienic conditions has been established but drug treatment is still pending. Therefore, study has been defined to form the potential phytotoxic and phytochemicals for the inhibition of COVID-19. Catechins and Epigallocatechin gallate (EGCG) are active phytochemicals and are found in green tea and black tea. Both antiviral activities have been reported against single RNA viruses (Mhatre et al., 2021b). Polyketides (PKS) are phytotoxic secondary metabolites produced from bacteria, fungi, plants, and animals. These are usually biosynthesized through the decarboxylative condensation of malonyl-CoA derived extender units and are structurally a very diverse family of natural products with diverse biological activities and pharmacological properties (Xu et al., 2021). These PKS are phytotoxins has very severe effects on the of agrarian and forest plants causing significant economic losses. In this study, beneficial medicinal role of PKS and phytochemicals has been planned to explore against COVID-19.

Materials and Methods

A list of polyketides and phytochemical used as a Ligands in molecular docking are listed in Table 1. The structure of these ligands of study has been retrieved from PubChem (https://pubchem.ncbi.nlm.nih.gov/). The 3-D protein structures Protein Data Bank (PDB# 6M0J) of Angiotensin-converting enzyme 2 (ACE2) has been retrieved in pdb format from the websites https://www.rcsb.org/.

Initially, protein was prepared for docking after getting the 3D structure of protein in pdb format from PDB. The water molecules, bonded ligands, non-standard residues were removed by MOE-2014.0901. Then further energy was minimized. Dummies atoms was created in binding sites and saved the prepared protein in moe format. After that, ligand database was prepared from the already downloaded 3D structures in sdf format from Pub chem. The energy of structures in database was minimized for docking and saved in mdb format. Finally, induced fit model was used for docking of receptor and ligands. A Flowchart diagram has showed the process of in-silico study.

Results and Discussion

A molecular information of ACE2 protein has been calculated in silico for molecular docking and found five different binding sites from 2a to 2e with active residues are; 2a= Asn546, Ser420, Ser545, Asp543: 2b= Asn90, Thr92, Lys26, Val93: 2c= Asn 322, Met3232, Trp326: 2d= Asn53, Asn 58, Thr55, Glu57, Gln 340: 2e= Phe342, Asn343, Gly339. These sites have been labelled within Fig. 2. All these information was used for molecular docking and five binding sites because this information will help to accurate and reliable results of binding (Vilar et al., 2008). The results of dock showed very interestingly promised docking with all PKS and phytochemicals. The binding free energies of all PKS and phytochemicals are listed in Table 2. On the basis of molecular interactions mechanism, the results of ACRL Toxin II CID_131751033, ACRL Toxin III A CID_54724812 and ACRL Toxin I B CID_54720478, PKS have showed lowest binding energy (ΔG kcal/mol) as compared to other phytochemicals and PKS; ΔG= -7.5117, ΔG= -6.9663, ΔG= -6.3194 kcal/mol, respectively. All Pubchem downloaded compounds taking the top ranked poses according to their interaction with the basis of binding cavity of ACE2 protein and binding free energies.

A network of hydrogen bonds is predicted between one of the hydroxyl groups of the ACRL toxin I and the B chains of GlyB 496 and some other weak interaction was found between ligands and Glu A37, HisA 34. Similarly, all other interactions can be seen in Fig. 2. The complete hydrogen bond interactions along with other weak interactions are shown in 2D interaction of all four competitive inhibiting ligands are presented in 2D interaction (Fig. 3). According to this interaction, these compounds ACRL toxins (ACRL Toxin I, ACRL Toxin II and ACRL Toxin III), Lovastatin CID_53232 and Biscopyran CID_139585310 (Bolded in Table 2) occupied the active sites of amino acids residues of ACE2 protein, hence relatively can inhibit the infection of CVID-19. Fig. 3 shows the amino acids residues in 2D interaction of ACRL toxins (ACRL Toxin I, ACRL Toxin II and ACRL Toxin III), Lovastatin CID_53232 and Biscopyran CID_139585310 with ACE2 and can be tried for inhibiting COVID-19 infection as an drugs inhibitor.

Table 1: List of polyketides and phytochemical used as a Ligands in molecular docking

Sr#	Polyketides /phytochemicals	Source	References
1	Botryodiplodin CID_33701	*Botryodiplodia thebromae*	(Ramezani et al., 2007),
2	2,5-Furandimethanol CID_74663	*Stilbocrea macrostoma*	(Di Lecce et al., 2020)
3	ACRL Toxin I B CID_54720478 ACRL Toxin II CID_131751033 ACRL Toxin III A CID_54724812	*Alternaria citri*	(Gardner et al., 1985)
4	Afritoxinone A CID_57387366	*Diplodia africana*	(Evidente et al., 2012)
	Afritoxinone B CID_57387609	*Diplodia africana*	(Evidente et al., 2012)
5	Oxysporone CID_14841096	*Diplodia africana*	(Evidente et al., 2012)
6	Biscopyran CID_139585310	*Biscogniauxia mediterranea*	(Evidente et al., 2005)
7	Chenopodolan B CID_132940966	*Phoma chenopodiicola*	(Evidente et al., 2015)
8	Brefeldin A CID_5287620	*Alternaria zinnia*	(Vurro et al., 1998)
9	Isocladospolide B CID_11601051	*Cladosporium cladosporioides*	(Hirota et al., 1985)
10	(3R)-8-hydroxy-3-methyl-3,4-dihydroisochromen-1-one CID_114679 ((-)-Mellein)	*Aspergillus ochraceus*	(Moore et al., 1972)
11	Trans-4-Hydroxymellein CID_10262028	*Aspergillus ochraceus*	(Moore et al., 1972)
12	4-Hydroxymellein CID_44445003	*Aspergillus ochraceus*	(Moore et al., 1972)
13	Spaeropsidone CID_10820808	*Diplodia cupressi*	(Masi & Evidente, 2021)
14	Sphaeropsidin A CID_51361447	*Diplodia cupressi*	(Masi & Evidente, 2021)
15	Lovastatin CID_53232	*Aspergillus terreus*	(Patil et al., 2011)
16	(2E,4S,6E,11R)-4,11-dihydroxydodeca-2,6-dienoic acid CID_122186298	*Cladosporium sp. TZP29*	(Zhu et al., 2015)
17	(2E,11R)-11-hydroxy-4-oxo-2-dodecenoic acid CID_10846956	*Cladosporium sp. TZP29*	(Zhu et al., 2015)
18	Catechins CID_1203	*Camellia sinensis*	(Zillich et al., 2015)
19	EGCG CID_65064	EGCG CID_65064	(Zillich et al., 2015)

Table 2: Binding free energies of docking with phytochemicals and PKS

Phytotoxin/Phytochemicals	ΔG kcal/mol
Catechins CID_1203	-5.4468
EGCG CID_65064	-5.9428
2,5-Furandimethanol CID_74663	-5.4007
ACRL Toxin I B CID_54720478	**-6.3194**
ACRL Toxin II CID_131751033	**-7.5117**
ACRL Toxin III A CID_54724812	**-6.9663**
(3R)-8-hydroxy-3-methyl-3,4-dihydroisochromen-1-one CID_114679 ((-)-Mellein)	-4.4383
Trans-4-Hydroxymellein CID_10262028	-4.4737
Spaeropsidone CID_10820808	-5.1271
Oxysporone CID_14841096	-4.6572
4-Hydroxymellein CID_44445003	-4.6917
Sphaeropsidin A CID_51361447	-4.15981
Afritoxinone A CID_57387366	-4.1705
Afritoxinone B CID_57387609	-4.9033
Biscopyran CID_139585310	**-6.7564**
Botryodiplodin CID_33701	-4.7286
Brefeldin A CID_5287620	-5.5312
Chenopodolan B CID_132940966	-4.9009
Lovastatin CID_53232	**-6.286**
(2E,11R)-11-hydroxy-4-oxo-2-dodecenoic acid CID_10846956	-5.5578
Isocladospolide B CID_11601051	-5.8242
(2E,4S,6E,11R)-4,11-dihydroxydodeca-2,6-dienoic acid CID_122186298	-6.3129
Cladospolide F CID_122186299	-5.9142

Moreover, a literature survey on the ACRL toxins has reported the data about mechanism of toxicity like brown spot disease on lemon and citrus species. Reported data describes the biological activity of ACRL toxins may be due to the mixture of keto and enol tautomers and furthermore, readily undergoes decarboxylation (Xu et al., 2021). No literature was found about the toxicity of ACRL toxins Lovastatin CID_53232 and Biscopyran CID_139585310 in animals. Because these are (fungal polyketides) secondary metabolites produced by fungus can infect only on plants (Evidente et al., 2005). So, they are host specific toxins and are toxic to specific plants that host the pathogens (fungus), but have lower phytotoxicity on non-host plants compounds (Xu et al., 2021). Besides this, few PKS have some medicinal importance, such as Lovastatin CID_53232 are used for lowering lipids, blood cholesterol and reduce the risk of cardiovascular disease (Aronson, 2015).

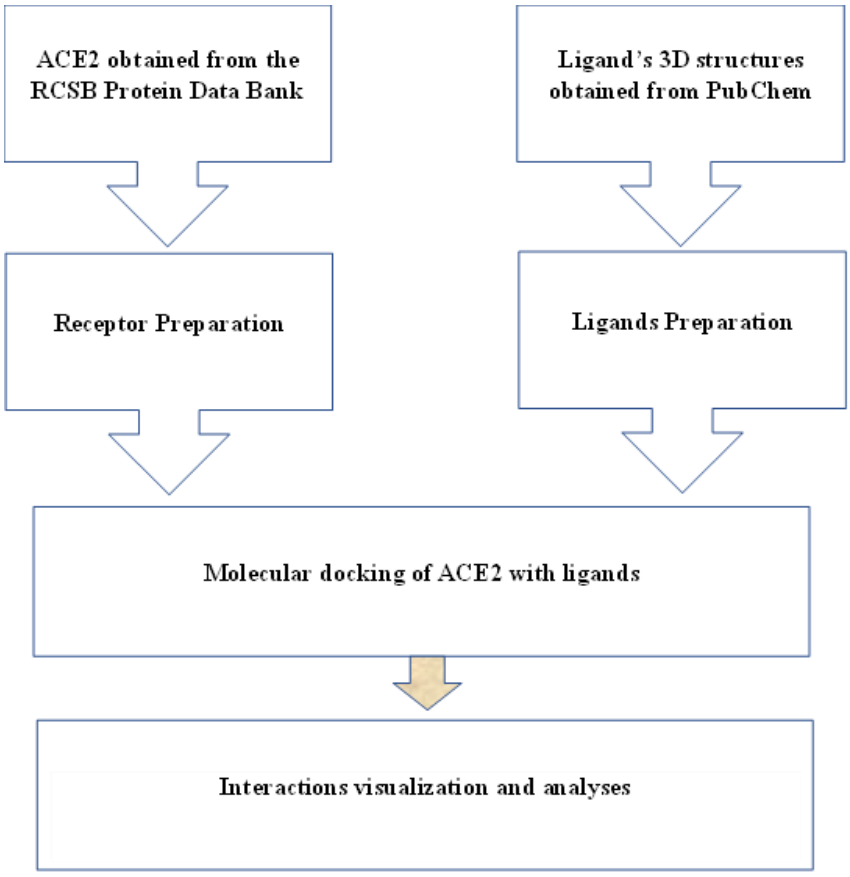

Fig. 1: A Flowchart diagram has showed the process of *in-silico* study.

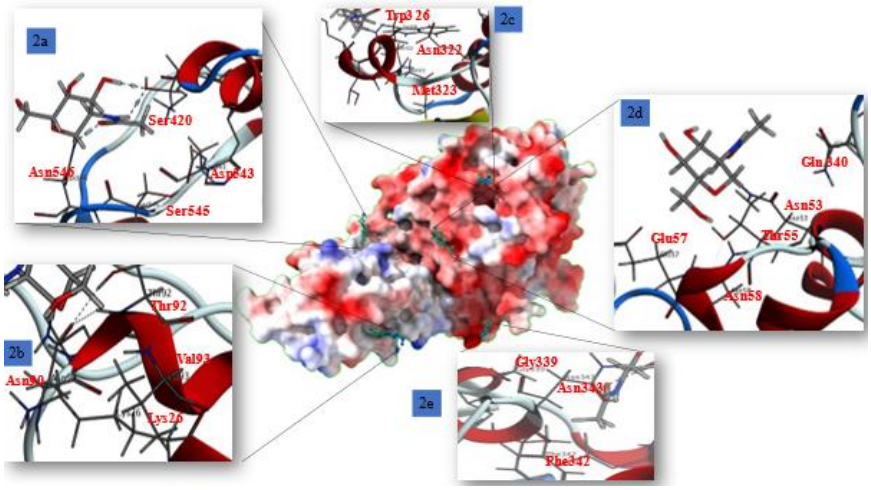

Fig. 2: A view of ACE2 and its active sites. The important residues of active sites from 2a to 2e are labeled.

Selected phytochemicals (Catechins CID_1203, EGCG CID_65064) have relatively weak interaction than ACRL toxins (ACRL Toxin I, ACRL Toxin II and ACRL Toxin III), Lovastatin CID_53232 and Biscopyran CID_139585310, and was higher than all others PKS. Literature has showed the advanced medicinal activities of phytochemicals as compared to PKS. By this relatively comparison, PKS should also search for the medicinal values, because they have on toxic effect on animals. These PKS have greater inhibiting interaction might be suggested on the bases of their pathogenic effect on plants as compared to phytochemicals.

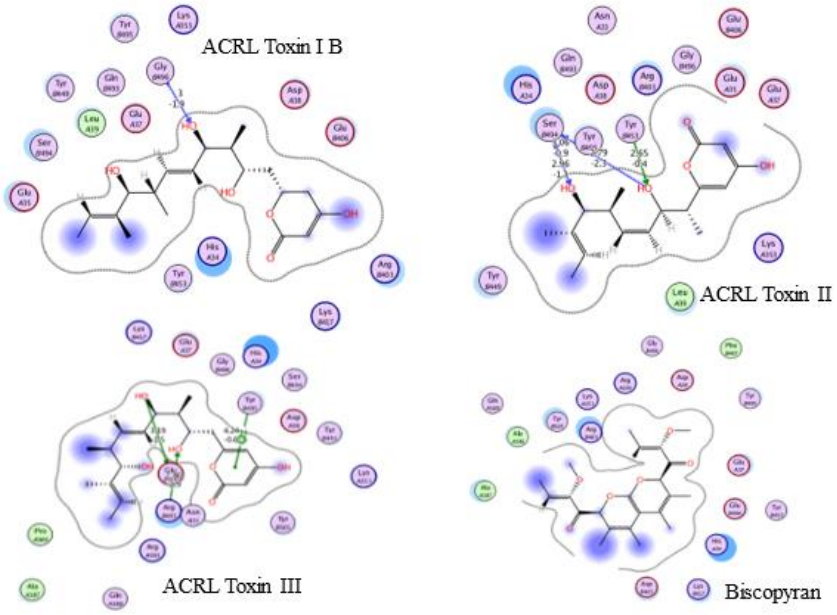

Fig. 3: ACE2 molecular docking studies and 2D interaction of ACRL toxins and Biscopyran and ACE2

Conclusion and Future Perspective: Fungal secondary metabolites are pathogenic polyketides (phytotoxic) and can toxic to specific plants. That's why, it can be searched for the medicinal importance for animals. Presently, in silico study, these polyketides (ACRL toxins, Lovastatin and Biscopyran) have showed higher inhibiting interaction with ACE2 protein as compared to tested phytochemicals (Catechins and EGCG). This will help the investigator for the exploration of these chemical practically on the animals with condition approval of authority.

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