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Molecular Docking Studies of Natural Polyphenolic Compounds with COVID-19 Viral Proteins Responsible for Antibiotic Resistance in Viral Pathogens to Prevent Virus Assembly: *In Silico* Computational Study

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Abstract: In order to distinguish possible hits that can inhibit the COVID-19 effects, virtual screening of natural polyphenols (PPs) was carried out by molecular docking (MD) and simulations *in silico* ADMET and drug like forecasts. Considering the medical relevance literature released, 4 phytochemicals (PC's) have been chosen with analogous PPs to scan the possible inhibitors for the replicase polyprotein 1ab therapeutic protein targets. The experiments *in silico* computing showed the efficacy of PPs such as ellagitana against the COVID-19 target proteins.The protein-ligand interaction analysis found that the proteins in the target proteins associate these PC's with the amino acid residues. The central structure of these possible hits can then be used to further optimise COVID-19 drug design. Also, medicinal plants that contain these PCs can be used to produce appropriate therapeutic approaches for conventional therapies like Strawberry (*Fragaria x ananassa*), Kiwi fruit (*Actinidia chinensis*), Litchi (*Litchi chinensis*) and Durian fruit (*Durio zibethinus*).

Keywords: *In silico* docking, ADME, COVID-19, Polyphenols, Rrplicase Polyprotein 1 ab, COVID-19

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Introduction

Protein-peptide interaction molecular docking (MD) experiments are a time-consuming and demanding process because peptides usually have greater flexibility than protein and appear to follow multiple conformations. Several benchmarking experiments have been undertaken on interactions between protein, protein and acid ligand docking (Savarino, 2007; Ulens *et al.,* 2009; Wang *et al.,* 2010). However, for protein peptide complexes in the literature a number of MD approaches have not been rigorously validated (Chen and Pohlhaus, 2010).The creative method of discovering new medicines is based on knowledge of the biological objective, also called the rational drug design (DD) or simply rational design (Mihăşan, 2012). The medicine usually is a small

organic molecule that stimulates or prevents the action of a biomolecule like an enzyme, and in turn results in a patient's medicinal advantage. In the fundamental sense, the designing of small molecules requires the architecture, which is complementary to the biomolecular objective with which they interact (Sadeer *et al.,* 2020).

Drug architecture mostly depends on computer simulation methods, although not generally. This modelling is also called the computer-aided design of medicines (Patil *et al.,* 2019). Finally, the design of medicines based upon understanding of the biomolecular objective's three-dimensional structure is known as structural DD (Patil *et al*., 2019). On a certain degree the term "DD" is an error. Ligand design is the true meaning of DD (i.e. design of a small molecule that will bind tightly to its target) (Sandhaus *et al.,* 2018). While modelling techniques for binding affinity are very promising, many other features are necessary for a ligand to become a safe and effective drug, such as bioavailability, metabolic half-living, lack of secondary effects etc. (Hayes *et al.,* 2011). Other features also have difficulty with rational drug design strategies (Mahiout *et al.,* 2018). With this in mind, we agreed to use the ligand and protein chosen as shown in Table 1 for the *in silico* MD and ADME toxicity.

Materials and Methods

The tools and databases used for the *in silico* MD and ADME study are-- PDB (Fig. 1), RasMol (Fig.2), PubChem (Fig. 3), ChemSketch (Fig. 4), Argus Lab (Fig. 5), Pymol (Fig. 6) and PreADMET (Fig. 7).

Results and Discussion

A coronavirus (CV) is a type of common virus that causes a nose, sinus or upper jaw infection. The CV 3-D (1O5S) structure has been downloaded from the PDB website. The compound structure for Ellagitannin, Gallic Acid, Epicatechin and Cinnamic Acid (ligands) was drawn with MDL-Mol format ACD ChemSketch. The 3-D protein structure (ReplicasePolyprotein 1ab) was connected to 4 ligands using the programme ArgusLab. The results of the MD were studied by means of a simulation instrument. The interactions between ligands and replicas Polyprotein 1ab were found in a silico MD sample, in order to estimate the minimum binding power (kcal/mol) (Table 2; Fig. 8). The findings suggest that the protein and ligands are linked to each other. In the four ligands, the Ellagitannin ligand has a good docking score of -11.46 Kcal/Mol for Replicase Poly protein 1ab. The MD is also true when 10 hydrogen (H_2) bonds are formed between them. Finding better medications for the COVID-19 process would also promise more research on the molecular dynamics and the QSAR through successful inhibition of this enzyme.

Validation can also be authenticated by means of wet laboratory experiments with the appropriate breed of animal. This experiment will pave the way for the new natural medicinal drug COVID-19. The aim of ligand protecting is to predict the major binding ligand models with a protein of known 3D structures. Ligand binding is the first step in and thus for inhibition of enzyme reactions. Therefore, the basis for a realistic approach to DD can be described in rigorous contact between small molecules and proteins. MD is now an efficient and cheap way of searches for a new lead compound, both structurally-based and link-based.

Molecular antiviral compounds against this targeted protein, including ReplicasePolyprotein 1ab, were successfully identified. The docking results have shown that each protein and ligand has a binding relationship that has been confirmed by hydrogeal connection between the proteins and ligand (Pollastri, 2010). Lipinski's rule also suggests the correct treatment medicine for ellagitannins. The findings show precisely how the ligands and proteins interact (Zhang *et al*., 2007; Alex *et al.,* 2011). Thus, silicon molecular docking and ADME experiments indicate that ellagitannins can also be used for the treatment of multiple diseases as possible and green therapeutic agent. Further, the effects of the ADME and drug-like

Table 1: List of PC's screened for drug-like properties dependent on *in silico* and ADMET

S.No.	Compound	Sources	Targeted disease protein
1	Ellagitannins	Strawberry (*Fragaria x ananassa*)	Replicase Polyprotein 1ab
2	Gallic acid	Kiwi fruit (*Actinidia chinensis*)	
3	Epicatechin	Litchi Chinensis	
4	Cinnamic acid	Durian fruit (*Durio zibethinus*)	

Fig. 1: PDB Home page.

Fig. 2: RASMOL Home page.

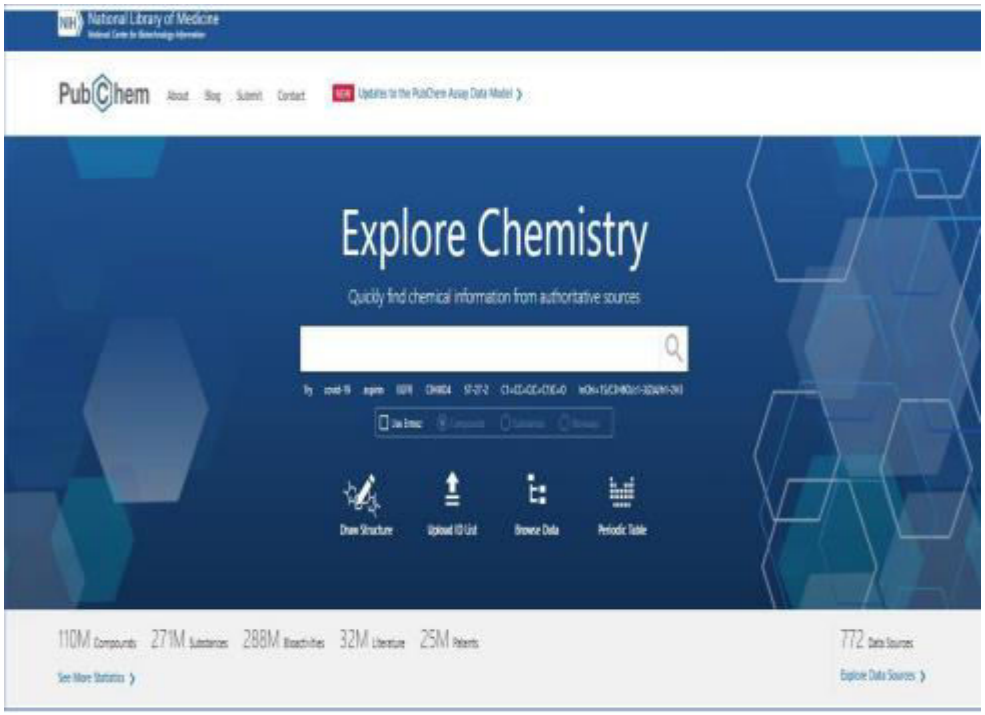

Fig. 3: PUBCHEM Home page.

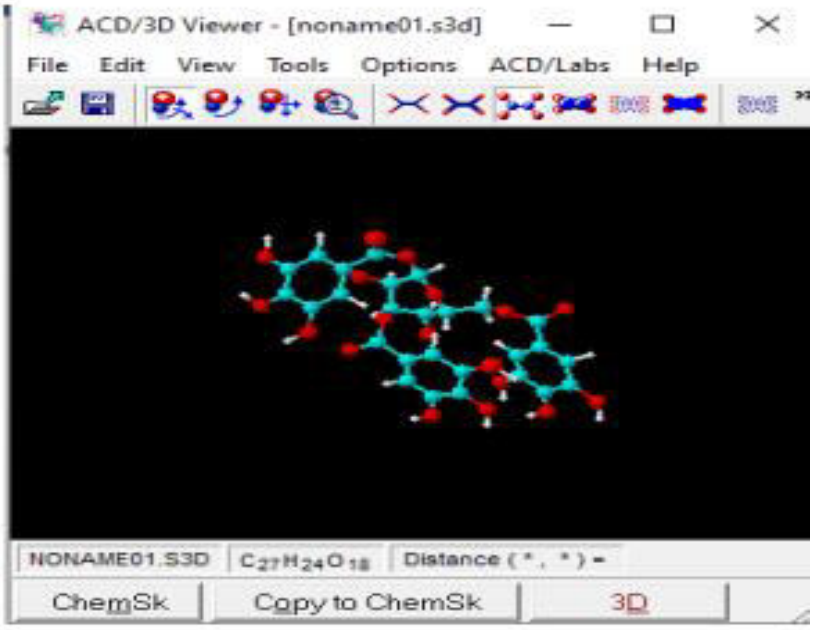

Fig. 4: CHEM Sketch Home page.

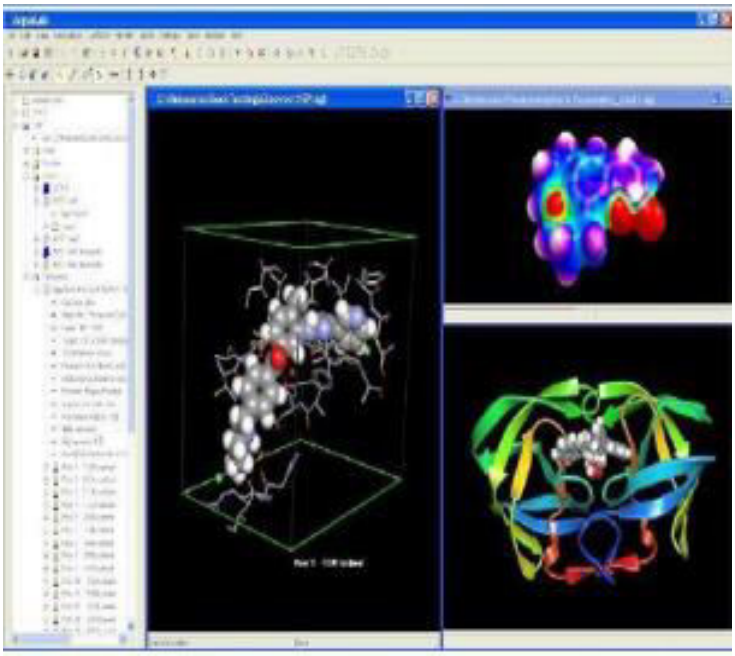

Fig. 5: ARGUS lab Home page.

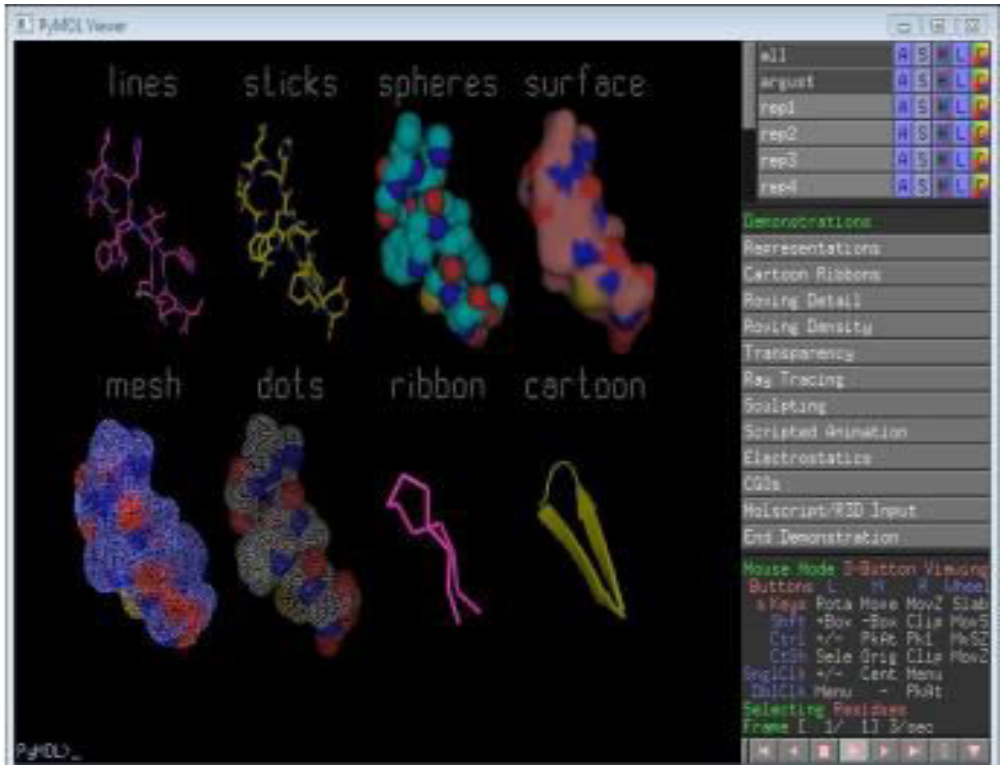

Fig. 6: PYMOL Home page.

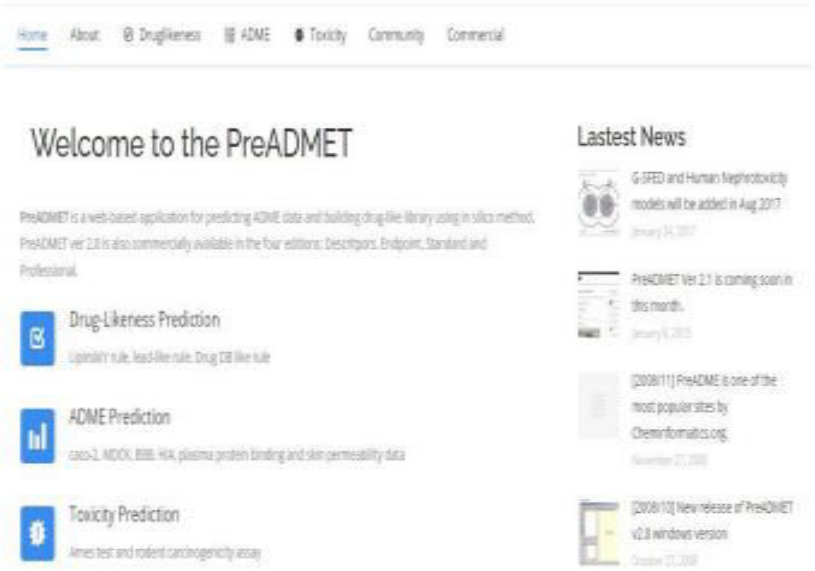

Fig. 7: Pre ADMET Home page.

Table 2: Docked complex of selected ligands and protein

Name of the ligand	Protein	Docking score (Kcal/Mol)	H-Bond
Ellagitannins	Replicase Polyprotein 1ab	-11.46	10
Gallic acid		-8.98	3
Epicatechin		-9.37	2
Cinnamic acid	No interaction		

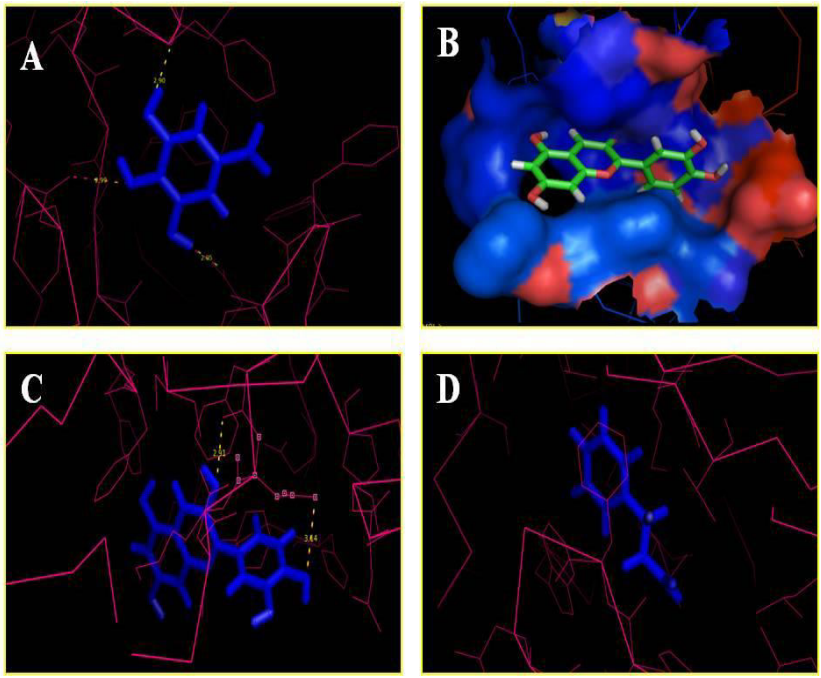

Fig. 8: Docked complex of Ligand A-Ellagitannins, B-Gallic acid, C-Epicatechine and D-Cinnamic acid against COVID-19 protein ReplicasePolyprotein 1ab.

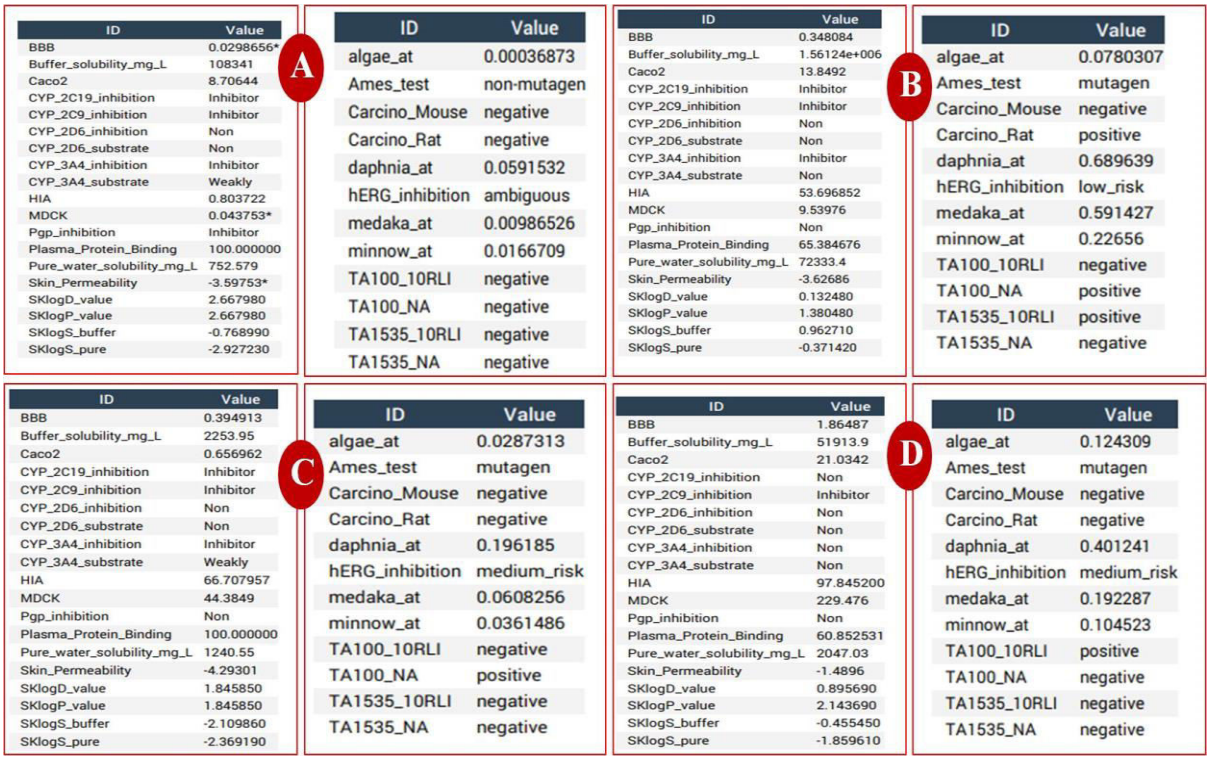

Fig. 9: ADME toxicity prediction of Ligand A-Ellagitannins, B-Gallic acid, C-Epicatechine and D-Cinnamic acid.

properties showed that the 4 ligands have healthy, expected orally bio-available, less toxic and good absorption characteristics (Fig. 9). The results of this study reinforce the importance of such compounds as potential leads in the treatment of viral conditions and could be helpful in further development and synthesising more potent candidates for medicines. In addition, the thesis facilitated an analysis of the proposed engineered compounds, both *in vivo* and *in vitro*, to verify the computer results.

Conclusion

In conclusion, the molecular docking binding interaction of ellagitannins, gallic acid, Epicatechine and cinnamic acid compounds (Replicase polyprotein 1ab) with viral protein effects is beneficial for manipulating and developing a new medication with improved COVID-19 inhibitory function. Compared to the other three substances Ellagitannins demonstrated a higher ability for docking. Ellagitannins are also one of the safest antiviral medicines for the treatment of viral conditions. Further evidence of its accurate collection as an antiviral medication is provided by wet laboratory experiments.

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