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Computational studies of Some Phytochemicals against COVID 19 through Molecular Docking Approach

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Abstract

COVID-19is declared as a pandemic The World Health Organization declared COVID-19 as a pandemic on March12th 2020 and it's very difficult to control this pandemic because there is no active vaccine or drug accessible for corona virus. Therefore, the objective of preset study is to analyze the inhibitory action of bioactive molecules from medicinal plants on 6W63 protein from protein data bank by computational docking studies and compare the result with recent reported inhibitory effect of chlorquine and hydroxyl chloroquine. It is well recognized that there is no available of efficient vaccine or drug for corona virus. We performed computational studies of phytochemicals versus Covid-19 main protease (PDB ID 6W63) with Molegro Virtual Docker 2013.6.0. (MVD). In our study active ingredients of Allicinof Allium sativum (Binding energy: -5.61 kcal/mole) shows better results than Chloroquine and Hydroxyl Chloroquine with minimum side effect. Based on binding energy score and ADMET studies of under examine compound, we compare the ADMET studies of reference compounds, and it is our suggestion that these compounds can be analyzed against corona virus and after that it can used to develop antivirus drug.

Keywords: SARS-CoV-2, Coronavirus, COVID-19, Moleculardocking, Phytochemicals, protein Data Bank Id (PDBid), Human Intestinal Absorption (HIA)**.**

Introduction

SARS-Cov-2 (several acute respiratory syndrome corona virus - 2) which in common language known as novel corona virus (2019 nCoV) now has become pandemic disease, it dramatically spread throughout the world from Wuhan (China) in the month of December 2019[1]. If we deeply examine, we will find that COVID 19 is changing its sequencing from a long time, in 2002 a disease SARS-Co (several acute respiratory syndrome corona virus) was the first time it started to spread but it was not such infectious. The World Health Organization declared COVID-19 as a pandemic on March 12th2020[2]. As per recent statistics that the 22.6 M confirmed cases of corona and 792K confirmed death due to corona in all world and in Indian scenario 625544 are confirmed corona positive cases and 18213 deceased due to this pandemic[3]. Thus, there is an urgent need for an effective treatment of corona patients, so identify active anti-viral agent but drug discovery is a multiple process with a high failure rate, high cost and its take time for the development of new molecules into the clinical candidate. Herbs which are used in ancient Indian medicine like *Allium sativum, Zingiber officinale, Piper nigrum, Syzygium aromaticum, Cinnamomum verum, Ocimum tenuiflorum*, have active ingredients which shows potential inhibition towards this novel corona virus. Recent report said that corona virus is single strain positive sense RNA virus that possess significant viral RNA genomes[4]. Even Though SARS-COV-2 is categorized into the beta corona virus group, it is different from MERS cov and SARS cov. Researchers reported that traditional Indian medicinal plants have major consideration because they include bioactive compounds that could be used for formal drug against several diseases[5]. The recent development of the novel pathogenic SARS-corona virus 2 (SARS-CoV-2) is responsible for this global pandemic[6] and there is an urgent need to identify active antiviral agents. Given the global health emergency, drug repositioning is the most consistent option to design an efficient therapy for infected patients without delay[7-8].

Therefore, the objective of preset study is to analyze the inhibitory action of functioning bio molecules from medicinal plants on 6W63 protein from protein data bank by computational docking studies and compared the result with recent reported inhibitory effect of chlorquine and hydroxyl chloroquine which used to fight pathogenic human corona virus. In our study some active ingredients of *Allium sativum* shows better results than Chloroquine and Hydroxyl Chloroquine with minimum side effect. In ancient Indian Ayurveda these herbs were used as an effective medicine for several common diseases[9-10].

Materials and methods

Retrieval of Protein: The three-dimensional crystal structures of Covid-19 main protease (PDB ID 6W63) determined by X-

ray crystallography had been retrieved from RCSB Protein Data Bank at atomic resolution 2.10 Å[11]. The water, useless residues and chains were manually deleted from the protein and saved in PDB format, and it was imported in the Molegro Virtual Docker 2013.6.0(MVD).

Retrieval of Phytochemical ligands: The structure of ligands is taken from PubChem data bank. The two-dimensional structures of reported ligands illustrated in Table-1. The structure drawn on Chem Sketch and energy minimization of compounds done using chem. sketch software then saved it in mol files which further used in docking procedure in MVD software.

Molecular Docking: **2.3.1 Cavity recognition and collection:** Probable active site for target main protease of Covid -19 (PDB Id 6W63) of attention had been determined with the help of MVD software.

Docking: For obtaining population of potential orientation and finding suitable binding site of ligand, we used computational docking. The molecular docking of SARS CoV-2 protein with the designated phytochemicals was carried out in Molargo Virtual Docker software (MVD)[12]. The ligands were prepared in MVD software and protein 6W63 was loaded in PDB format by water removal, H-atom. The grid resolution was 30 A^0. The grid center was located on the active site of the protein at X=-20.46, Y=18.11, Z= 26.91. The best binding activity was carefully chosen from a set including ten interacting poses after selection of ligand and protein. The docking score of observed phytochemicals with protein were related with chloroquine and hydroxychloroquine.

Drug likeness and ADMETSAR prediction: The quantitative estimation of absorption, deposition, metabolism, excretion and toxicity (ADMET) profile of selected phytochemicals ligands were predicted computationally by applying swiss ADME software[13]. The result of software shows that the molecular weight (MW) of phytochemicals is below 500, log P value is below 5. These phytochemicals were observed to agree with Lipinski's rule of 5, so one compound shows 1 violation of Lipinski's rule and other shows zero violation of Lipinski's rule.

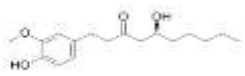
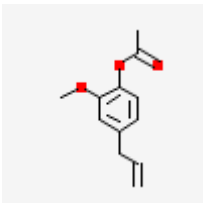
Table-2 shows Log S value. Solubility of the ligand is confirmed by Log S value which is found between -6.5 and 0.5. Phytochemicals studies shows Log S value between prescribe range. Acetyl eugenol (-4.50) and curcumin (-3.84) shows maximum Log S value. With the help of Blood Brain Barrier permeability (BBB), the permeability of membrane can be evaluated, the normal range of BBB values for a perfect drug candidate range among -3.0 and 1.2. All the phytochemicals which are used in this study have BBB value under this range.

Results and discussion

In structure-based drug design, now- a -days molecular docking is one of the best methods, due to its capacity to calculate the binding conformation of ligands to appropriate target binding site. In recent scenario, we can save a large amount of energy, time, and expenses by the examined and marked of phytochemicals of herbs with this approach and expenses related to CADD can be saved[14]. Presently, there are no effective treatments available to cure COVID-19 virus, and so, recognition of probable drug goals is immediately desired.

The parameter used for the docking analysis are Mol Dock score, Rerank score and H-Bond interactions (binding energy). In our study, Chloroquine and Hydroxychloroquine were chosen as a reference drugs because these are being used as an agent under clinical investigation for the treatment of COVID-19[15]. On the basis of docking score and bonding interaction (Table-1), the six tested ligands along with the reference drugs with respect to target protein have been discussed in this study.

Table-1: Two-Dimensional structure with docking score of the phytochemicals.

Phytochemical Name	Plant Source	2- D Structure	Energy Or Moldock Score
Gingerol	*Zingiber officinale*		-6.30
Acetyl eugenol	*Syzygium aromaticum*		-5.14

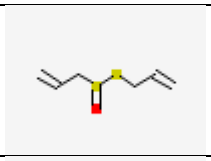
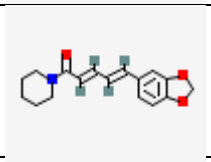
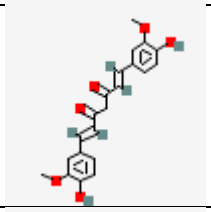
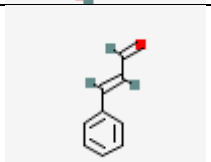
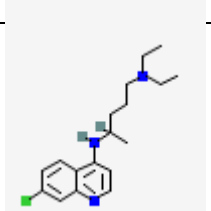
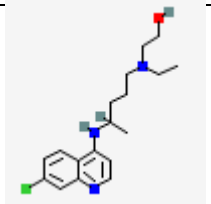
Allicin	*Allium sativum*		-5.61
Piperine	*Piper nigrum*		-28.77
Curcumin	*Curcuma longa*		-44.33
Cinnamaldehyde	*Cinnamomum verum*		4.41
Chloroquine	--		-5.4
Hydroxychloroquine	--		-5.7

Table-2: Physicochemical properties of selected phytochemicals.

Ligand	MW (≤500) g/mole	Log S	HIA	BBB	Rule of 5 violation	Lipinski 's Rule
Gingerol	249.39	-2.96	High	Yes	0	Yes
Acetyl eugenol	200.32	-4.50	Low	Yes	1	Yes
Allicin	138.25	-0.87	High	Yes	0	Yes
Piperine	285.34	-3.74	High	Yes	0	Yes
Curcumin	388.45	-3.84	High	No	0	Yes
Cinnamaldehyde	134.18	-1.74	High	Yes	0	Yes
Chloroquine	268.44	-6.35	Low	No	1	Yes
Hydroxychloroquine	296.45	-6.35	Low	No	1	Yes

The binding energy of Acetyl eugenol of *Syzygium aromaticum* (-5.14kcal/mole) and Allicin *of Allium sativum* (-5.61 kcal/mole) were found to be similar then the reference drugs. All six ligands were docked into binding pocket of this protein and based on docking score Gingero l(-6.30kcal/mole), Acetyl eugenol (-5.14kcal/mole), Allicin (-5.61 kcal/mole), Piperine (-28.77kcal/mole), Curcumin (-44.33kcal/mole), Cinnamaldehyde (4.41 Kcal/mole). The results show that the docking score of observed phytochemicals are higher as compared to the reference drugs. Two-dimensional structure of docked ligand molecules along with docking score represented by Table-1. The specificity and affinity of protein ligand complex[16] has decided by Hydrogen bonds so Hydrogen bonds perform significant role.

Evaluation of Drug likeness: The pharmacological importance of a ligand is evaluated on various properties like drug bioavailability, drug-likeness or ADMET etc. These properties are estimated by certain physicochemical and structural properties so that all six hit ligands were anticipated for their drug like nature with Lipinski's rules of five by swiss ADME software. The pharmacokinetic properties of a ligand are Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET). With the help of swiss ADME software, it is defined that the molecular weight of phytochemicals are 500.the value of log P is under 5, Hydrogen bond acceptors number are in between 10. All phytochemicals under this study, were go along with the Lipinski's rule of 5.

The relative ADMET profiles of the selected phytochemicals are demonstrated by Table-2 and it compares with both references. Log S show the solubility of the ligand which has in perfect ranges between -6.5 and 0.5. All the observed phytochemicals are displaying Log S values among these scales. Blood-Brain Barrier permeability (BBB) value for all the observed phytochemicals was like the reference molecule. The computational BBB value is very important for drug candidate molecule, this corresponds to its entrance into central nervous system. The normal range of BBB values for a perfect drug candidate is in between -3.0 and 1.210. All the observed phytochemicals show their BBB value under this range. Acetyleugenol shows the value of Human Intestinal Absorption (HIA) similar as the HIA value of reference molecules. If a compound has the HIA% is less than 30%, it is classified as HIA- otherwise; it is classified as HIA+. Hydrophobic, aromatic, a hydrogen bond acceptor, a hydrogen bond donor, negative and positive functional groups are basic features of a typical pharmacophore molecule. The pharmacophore study of observed phytochemicals shows that it's have all basic features as like the reference.

The comparison of pharmacophore features indicates that these compounds can be developed as drug candidates against Corona virus.

Discussion: As know that natural products can be used both ways to prevent viral disease and stop the virus from spreading. I used the recently released crystal structure of COVID 19 protease (PDB ID 6W63) and low hazard herbal medicine for docking analysis. It's found six plants such as *Zingiber officinale, Syzygium aromaticum, Allium sativum, Curcuma longa, Cinnamomum verum, Piper nigrum* have such compounds showing better and considerable binding energy against these receptors.

Better binding energy with the target shows by observed two phytochemicals Acetyleugenol and Allicin. In this study we have also compared pharmacophoric features of observed phytochemicals and reference compounds. A lot of medicinal plants are existing which have antiviral, antibacterial and antifungal activity, certain studies show that these plants have capacity to increase the immune system[17]. So, the phytochemicals of these medicinal plants can be used as an inhibitor for Corona virus.

Conclusion

On the basis of binding energy score and ADMET studies of under studies compounds , we compare the ADMET studies of reference compounds and we advise that these compounds can be tested against corona virus and used to develop active antivirus drug, two phytochemicals Acetyl eugenol and Allicin gave better binding energy with the target, The binding energy of Acetyl eugenol of *Syzygium aromaticum (*-5.14 kcal/mole) and Allicin *of Allium sativum(-5.61* kcal/mole*)* were found to be similar then the reference drugs. So, we propose that these compounds can be investigated against corona virus and used to develop antivirus drug.

List of abbreviations: PDBid- (protein Data Bank Id), HIA- **(**Human Intestinal Absorption).

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