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In-Silico Study of Natural Herbal Medicines against CORONA VIRUS Proteins

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***Abstract*— SARS-CoV-2 corona virus is known as novel corona virus majorly affecting normal breathing process in humans. It has caused global pandemic situation due to its high rate of infection from people to people and leads to several millions death worldwide. The Aim of this present study is to identify few phytochemicals, as potential drug candidates against viral target proteins RNA dependent RNA polymerase and ACE2 receptor through in-silico approach.**

Material and Methods-- Five natural herbal compounds and target proteins RNA dependent RNA polymerase (PDB ID-7BTF) and ACE2 receptor (PDB ID-3D0I) selected and retrieved from PubChem database and Protein data bank respectively. PatchDock server was used for molecular docking between phytochemicals and target proteins. SWISSADME server (http://www.swissadme.ch/) was used to predict solubility, target accuracy and pharmacodynamics property of the selected drugs by evaluating Lipinski's rule of five, which also suggests molecular permeation and oral absorption. And Discovery Studio tool was used to visualize and analysed all the results from PatchDock server.

Results-- The molecular docking study suggested that all five phytochemicals docked the predicted binding active site of target proteins via several non-covalent i.e. hydrogen bond, vander-waal interaction etc. Phytochemicals showed good docking score (curcumin-7BTF: 4796, curcumin-3D0I: 5004; Di-O-(2-Thienoyl) curcumin-7BTF: 6608, Di-O-(2-Thienoyl) curcumin-3D0I: 7810; quercetin-7BTF: 3996, quercetin-3D0I: 4492; glycyrrhizin-7BTF: 7924, glycyrrhizin-3D0I: 8824; glabridin-7BTF: 4876, glabridin-3D0I: 5242) with the target proteins RNA dependent RNA polymerase enzyme and ACE2 receptors. Among all, modified curcumin (Di-O-(2-Thienoyl) curcumin) and Glycyrrhizin showed best docking score as similar as referenced standard drug Remdesivir (remdesivir-7BTF: 6914, Remdesivir- 3D0I: 7980) indicating their antiviral properties. The drug-likeness properties of phytochemicals were determined and found to be within acceptable range according to Lipinski's rule.

Conclusion-- The docking results suggested that all phytochemicals showed good binding affinity against viral proteins RNA dependent RNA polymerase and ACE2 receptor. Curcumin and Glycyrrhizin could be a potential candidate as an antiviral Drug.

***Index Terms*— SARS-CoV-2, RNA dependent RNA polymerase enzyme, ACE2 receptor etc.**

I. INTRODUCTION

December 2019 was the outbreak period of coronavirus disease 2019 (COVID-19) originated in Wuhan, China. COVID-19 pandemic have an effect on all over the globe and affected around 210 countries in few week. [1]

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Several lacks of the people have been affected with this deadly disease and many of them have been died due to this corona virus-2. From 2002 onwards, we had countersigned the rise of three coronaviruses with distinct features, these are Severe Acute Respiratory Syndrome Coronaviruses (SARS-CoV), MERS-CoV and the SARS-CoV-2, causal agent of COVID-19 pandemic [2]. SARS-CoV-2 has very close phylogenetic similarity (aprox 89.1% nucleotide similarity) [3] with SARS- CoV virus (MG772933) [4] (genus Betacoronavirus) that had been previously been recognized in bats in China, hence it was also named as corona virus 2 (SARS-CoV-2) which mainly causes severe acute respiratory syndrome along with several other illness that might lead to death [3]. One, among several auspicious therapeutic strategies for eradication of virus infection is the search for RNA Dependent RNA Polymerase and spike protein inhibitors among plenty of natural compounds using molecular docking technique in order to obtain a herbal drug with minimal side effects. SARS-CoV-2 virus protein: spike protein and RNA Dependent RNA Polymerase protein plays an active role in viral infection and its transcription and replication, which made it very crucial as a target protein for SARS-CoV-2 virus.

A. Remdesivir (Compound CID: 121304016)

Remdesivir is a potentially used anti-viral therapeutic treatment for Ebola virus disease. In COVID 19 pandemic, this therapeutic agent has been approved for the treatment of severe COVID 19 patients who are on ventilators in ICU. Remdesivir has been synthesized and developed by Gilead Sciences Biopharmaceutical Company in 2017 as a cure for Ebola virus infection. Chemically this drug has been formulated from monophosphoramidate prodrug which was an adenosine analog. Remdesivir is absorbed into its active form that conceals the function of viral RNA dependent RNA polymerase triggering a fall into viral load [2].

B. Curcumin (Compound CID: 969516)

Curcumin [diferuloylmethane, 1, 7-bis (4-hydroxy-3-methoxyphenyl)-1, 6- hepta- diene-3,5-dione], is a distinguished acyclic diarylheptanoid which is known as the major component of turmeric powder from the rhizome of the plant curcuma longa [5]. Emergent evidence about the antiviral potential of herbal compounds made everyone curious to know about the effect of these compounds as a therapeutic agent against COVID 19 pandemic. Curcumin, the bioactive compound of turmeric is an excellent example among phytochemicals with diverse mode of actions. At

present curcumin is approved by the US food and drug administration (FDA) for several health benefits. Over 300

clinical trials that have been reported earlier, shows the beneficial and protective effects of curcumin against several diseases like inflammatory diseases, cardiovascular diseases, pulmonary disease, neurological diseases, liver diseases, and cancers. Curcumin has anti-viral property against many different viruses, possibly would be a therapeutic strategy for the COVID-19 infection. [6]

C. Di-O-(2-Thienoyl) curcumin (Compound CID: 45028269)

Di-O-(2-Thienoyl) curcumin was formulated by esterification of curcumin along with thiophene-2-carbonyl chloride [7]. It is modified form of curcumin that also have the same or even greater potential as an anti-viral drug as suggested by this research article.

D. Quercetin (Compound CID: 5280343)

Quercetin is isolated from the leaves and rhizomes of two varieties of Zingiber officinale (Halia Bentong and Halia Bara). Quercetin is abundant in both varieties. The significance of quercetin is of great interest due to its antioxidative and probable anticarcinogenic activities. Quercetin a flavonoid, that functions as reducing agents, free radical scavengers and quenchers of singlet oxygen formation as well as also work as anti- inflammatory molecule. Research shows that quercetin is also the main flavonoid component in ginger [8] as well as in onion and garlic [9]. Other important aspect of the use of quercetin compound is its anti-viral effect. It has no virucidal effect, but interferes with the replication of several viruses [10].

E. Glycyrrhizin (licorice): (Pubchem id- 128229)

Dried roots of Glycyrrhiza glabra have a distinctive odour and sweet taste. It shows anti-inflammatory, antioxidant and immunomodulatory effects. Glycyrrhizin is the major constituent of Glycyrrhiza glabra root. Glycyrrhizin is made up of glycosylated saponin that contains one molecule of glycyrretinic acid that have structural similarities with hydrocortisone, and two molecules of glucuronic acid. It has been endorsed for its numerous pharmacological effects like anti-inflammatory, anti-viral, anti-tumor, and hepatoprotective credentials [11]. This agent significantly reduced expression of pro-inflammatory cytokines: nuclear factor–κB, interleukin-1β and interleukin-6 [12]. By this way this drug also inhibit the condition of cytokine storm that could be responsible for several deaths related to SARS-CoV-2 virus.

F. Glabridin (Compound CID: 124052)

Licorice contains more than 20 triterpenoids and nearly 300 flavonoids. Among them Glabridin (GLD) is also the main active constituent of the licorice that possess anti-viral as well as anti-microbial activities [13]. Till now glabridin mainly exhibited antifungal activity on C. albicans so it is known as a potential antifungal agent [14]. But this study also suggests that this GLD also act as an anti-viral agent against COVID-19 infection.

II. METHODS

A. Structural retrieval of RNA Dependent RNA Polymerase and Spike proteins receptor (ACE2)

COVID-19 important structure RNA Dependent RNA Polymerase with PDB ID: 7BFT and SARS-CoV-2 viral spike protein receptor (ACE2) with PDB ID: 3D0I. The structures (PDB ID: 7BFT & PDB ID: 3D0I) were downloaded from PDB server (https://www.rcsb.org/) in its .pdb format. PDB is a repository for the X-ray crystallographic and NMR based structures of biological molecules mainly protein and DNA worldwide [15]. The 7BFT protein contains 4 chains: A, B, C and D which form a tetramer. There were several ligands associated with this protein so further select all of the ligands and delete from there and prepare protein for fresh docking analysis. The 3D0I protein also contains 4 chains: A, B, E and F which is also forming tetramer that was used for target preparation.

B. Structural retrieval of drugs from PubChem

The 3-dimensional (3D) structure of the ligands was taken from PubChem lead data base server (https://pubchem.ncbi.nlm.nih.gov/) in its .sdf format. PubChem is an open access chemistry database at the National Institutes of Health (NIH). PubChem merely contains small molecules (lead compounds) but also have macro -molecules like nucleotides, carbohydrates, lipids, etc. and also chemically-modified compounds. PubChem provide information about chemical structures, identifiers, chemical and physical properties, metabolic activities, toxicity, safety, patents and many others [16]. PubChem is a chemical substance and biological activities repository consisting of three databases, including substance, compound, and bioassay databases. All the herbal and chemical (remdesivir) ligand compounds were downloaded from PubChem database. The biologically active compounds used in the present study were Remdesivir (Compound CID: 121304016), Curcumin (Compound CID: 969516), Di-O-(2-Thienoyl) curcumin (Compound CID: 45028269), Quercetin (Compound CID: 5280343), Glycyrrhizin (licorice) (Compound CID: 128229) and Glabridin (Compound CID: 124052). Drug-likeness of these ligands have been predicted using SWISSADME server (http://www.swissadme.ch/) by evaluating Lipinski's rule of five, which suggests molecules with deprived permeation and oral absorption would have molecular weights > 500, >5 H-bond donors and >10 H-bond acceptor groups and C logP > 5 [17] [18].

C. Determination of Active Sites

Different amino acids present in the predicted active site of a protein were determined using the Biovia Discovery Studio Tool 3.5. Predicted amino acids exist in the active site would be used for docking precision analysis. Discovery Studio is offline 3D structures visualizer tool that make available all the aspects needed for the docking studies.

D. Docking studies

Retrieved all the ligand structures in its .sdf format and open it in Biovia Discovery Studio 3.5 tool and saved as in its .pdb format. Further 2 target proteins RNA Dependent RNA Polymerase and Spike proteins receptor (ACE2) have been retrieved from PDB database in .pdb format. There is no need of validation of these proteins because these are already well validated and then submitted to this database. Now these proteins are used for docking with its respective ligands using an online server Patchdock. The docking results would be analysed through Biovia Discovery Studio 3.5.

III. RESULTS

Two important proteins of the SARS-CoV-2 virus are RNA Dependent RNA Polymerase and Spike proteins adherent receptor ACE2 where one is responsible for viral replication in different epithelial cells and further most is ACE2 receptor which binds with SARS-CoV-2 viral spike protein and facilitates entry of the virus inside epithelial cells. All the drugs that have been taken for docking studies are used as herbal products for therapeutic use in several ailments mainly in viral infection treatment, so that's why these drugs have been selected to combat Covid-19 pandemic. .

A. Structures of Target proteins along with its predicted active site surface (RNA Dependent RNA Polymerase (a and b) and Spike proteins receptorACE-2(c and d))

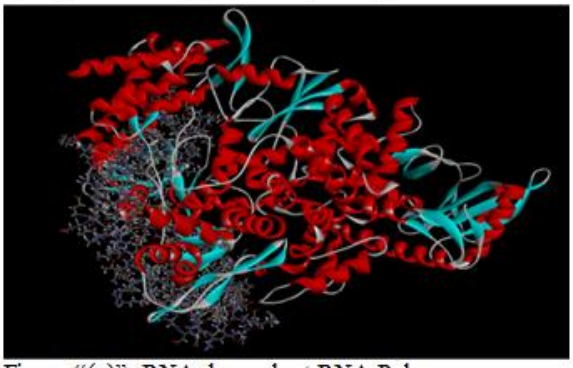


Figure "(a)"- RNA dependent RNA Pol

Figure "(c)"- ACE2 receptor

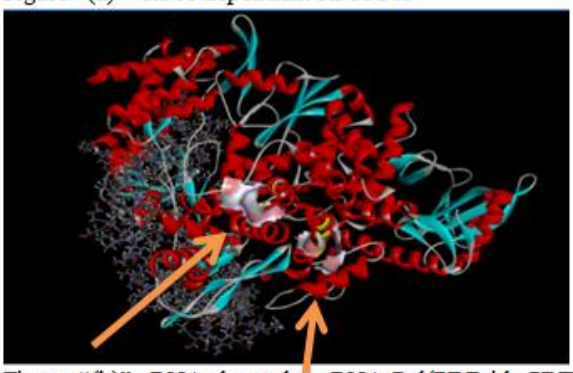


Figure "(b)"- RNA dependent RNA Pol(PDB id- 7BTF) along with predicted Active site surface view

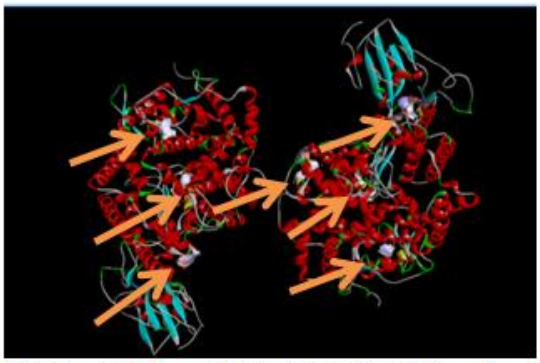
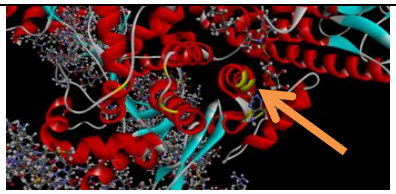
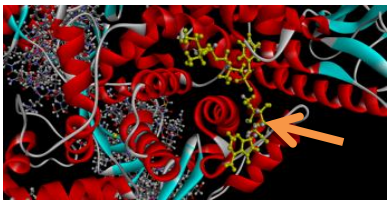
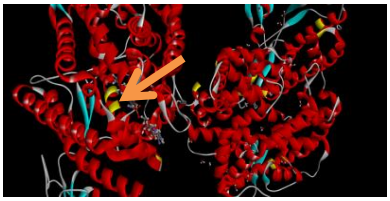
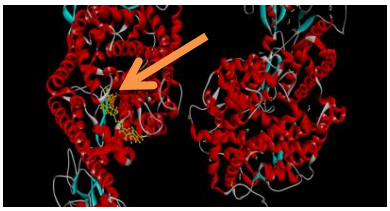
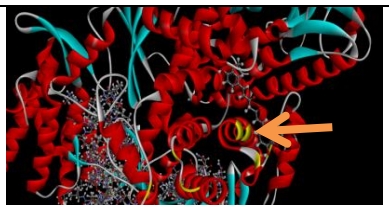
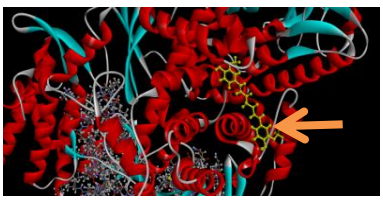
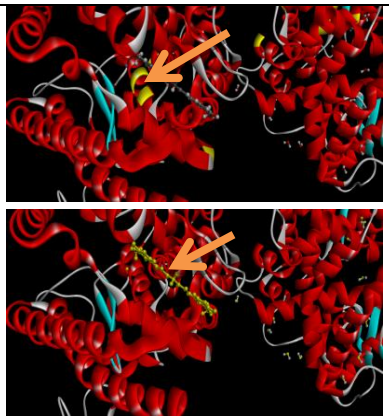
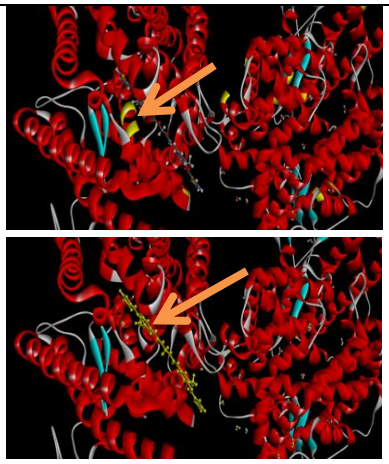
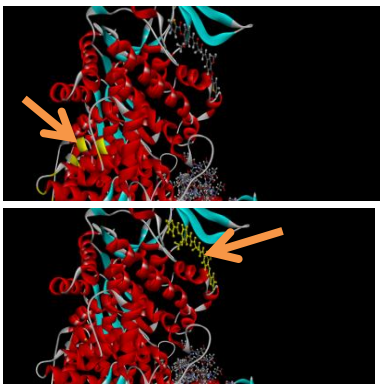


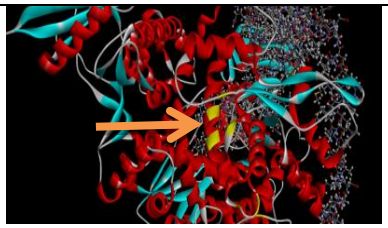
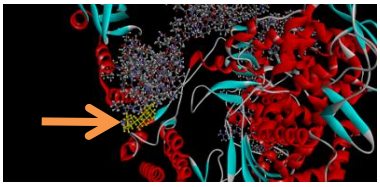
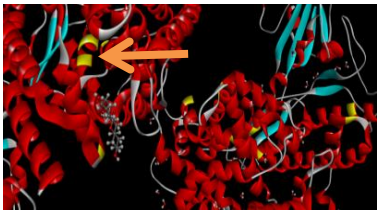
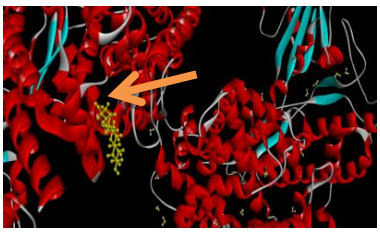
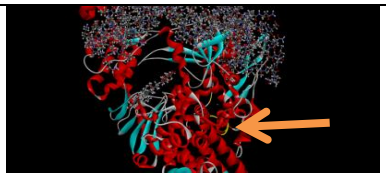
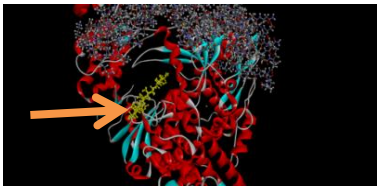
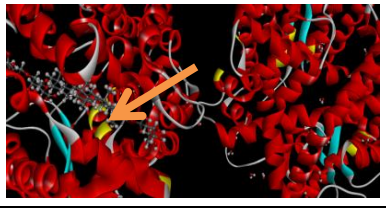
Figure "(d)"- ACE2 receptor(PDB id- 3D0I) along with predicted Active site surface view

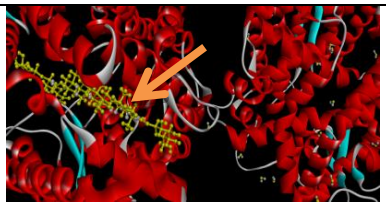
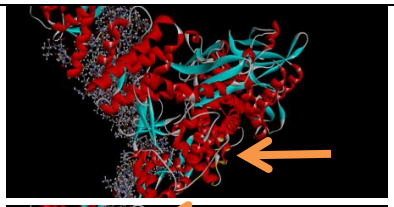
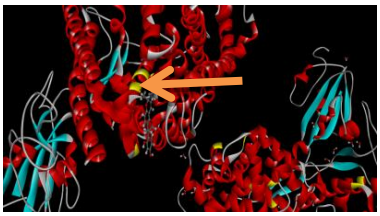
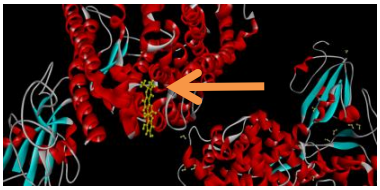
All drug candidates (herbal compounds) have been selected based on criteria suited to qualify Lipinski's rule of five. Selected ligands those did not experience more than 2 violations of Lipinski's rule, would have been used in this molecular docking study with both the target proteins. The drug'sproperties related to Lipinski's rule of five have been resulted in Table 1that shows all potential candidates were acknowledgedthrough Lipinski's rule of five.

Table 1:Properties of selected potential inhibitor candidates for COVID-19 related RNA dependent RNA polymerase and spike protein receptor ACE2 protein.

No	Ligand name	Pubchem Id	Molecular structure and its interaction with target protein	Properties (Lipinski's rule)	Values (Lipinski's rule)
1.	Remdesivir	CID: 121304016	  Target- 7btf Ligand- Remdesivir **D. score - 6914** Energy- **-253.69**   Target- 3D0I ACE2 Rec Ligand- Remdesivir **D. score - 7980** Energy- **-247.75**	Molecular weight (<500 Da) LogP (<5) H-Bond donor (<5) H-bond acceptor (<10) Violations Druglikeness	602.58 1.50 4 12 2 No
2.	Curcumin	CID: 969516	  Target- 7btf Ligand- Curcumin D. score - 4796 Energy- -203.61	Molecular weight (<500 Da) LogP (<5) H-Bond donor (<5) H-bond acceptor (<10) Violations Druglikeness	368.38 3.03 2 6 0 Yess

			 Target- 3D0I ACE2 Rec Ligand- Curcumin **D. score - 5004** Energy--**362.97**		
3.	Di-O-(2-Thienoyl) curcumin	CID:45028269	 Target- 3D0I ACE2 Rec Ligand-Di-O-(2-Thienoyl) curcumin **D. score - 7810** Energy- -**301.85**  Target- 7btf Ligand-Di-O-(2-Thienoyl) curcumin **D. score - 6608** Energy- **-225.33**	Molecular weight (<500 Da) LogP (<5) H-Bond donor (<5) H-bond acceptor (<10) Violations Druglikeness	588.65 5.83 0 8 1 Yess

4.	Quercetin	CID: 5280343	  Target- 7btf Ligand- Quercetin D. score - 3996 Energy- -106.86   Target- 3D0I ACE2 Rec Ligand- Quercetin D. score - 4492 Energy- -191.44	Molecular weight (<500 Da) LogP (<5) H-Bond donor (<5) H-bond acceptor (<10) Violations Druglikeness	302.24 1.23 5 7 0 Yess
5.	**Glycyrrhizin**	CID: 128229	  Target- 7btf Ligand- Glycyrrhizin **D. score - 7924** Energy- **-218.32** 	Molecular weight (<500 Da) LogP (<5) H-Bond donor (<5) H-bond acceptor (<10) Violations Druglikeness	822.93 1.55 8 16 3 No

			 Target- 3D0I ACE2 Rec Ligand- Glycyrrhizin **D. score - 8824** Energy--**275.12**		
6.	**Glabridin**	CID: 124052	  Target- 7btf Ligand- Glabridin D. score - 4876 Energy- -71.10   Target- 3D0I ACE2 Rec Ligand- Glabridin D. score - 5242 Energy- -221.26	Molecular weight (<500 Da) LogP (<5) H-Bond donor (<5) H-bond acceptor (<10) Violations Druglikeness	324.37 3.45 2 4 0 Yess

IV. RESULT DISCUSSION

SARS-CoV-2 virus related to a group of viruses that infected humans as well as vertebrate animals. This virus affects respiratory system (lungs), cardiac system (include heart attack and high BP) circulatory system (attack of cytokine storm) [19] and central nervous system [20] etc. of humans. The present docking study is focused on two important proteins, RNA dependent RNA polymerase and spike protein receptor ACE2 protein, as important target proteins used for COVID-19 treatment. PDB id- 7BTF and 3D0I is the important COVID-19 proteins those have been structured and deposited in PDB protein databank. RNA dependent RNA polymerase is important as virus replicating enzyme and ACE2 receptor facilitate entry of the Corona

virus inside the host cell of the human body and have been studied as a potential target protein to inhibit the spread of viral infection [21]. The discovery of the RNA dependent RNA polymerase and ACE2 receptor provides a great prospect to recognize potential drug candidates for treatment of Covid 19. In different viruses RNA dependent RNA polymerase play critical role in viral replication, used as a therapeutic target for the development of proper acting drug and ACE2 receptor facilitate entry of the virus inside the epithelial cells therefore it is also a crucial protein for targeting. Remdesivir (CID: 121304016) is a well-known inhibitor of RNA dependent RNA polymerase which is approved by Health ministry and authority to use against Covid patient [22]. Docking score of these two components (target & drug) is 6914 and free energy is -253.69. This drug is approved against RNA dependent RNA polymerase enzyme but in this study it is also showing that this drug is also interacting with ACE2 receptor with even good docking score 7980 and free energy is -247.75 that shows this drug has inhibitory effect on RNA dependent RNA polymerase enzyme along with ACE2 receptor protein. That may infer that Remdesivir not only affect RNA dependent RNA polymerase enzyme but also affect ACE2 receptor and by its coordinated action this drug is used to treat covid patients although this drug did not follow druglikeness properties. There is some herbal products those have greater efficiency to treat covid patients. Some of those herbal drugs have greater and significant docking score as well free energy score that shows these drugs could also be a treatment for covid-19 patients. Curcumin has docking score 4796 and free energy is -203.61 against target 7btf (RNA dependent RNA polymerase enzyme) as well curcumin also has docking score is 5004 and free energy is -362.97 against target 3D0I (ACE2 receptor). It shows that curcumin has greater binding affinity with ACE2 receptor than RNA dependent RNA polymerase enzyme for fighting against Covid-19. This result also shows that curcumin have more than one target to bind and manifest its therapeutic effects along with perfect druglikeness properties. That reflects curcumin exhibit significant potential for being therapeutic agent for Corona virus infected patients. Di-O-(2-Thienoyl) curcumin (modified curcumin) has docking score 6608 and free energy is -225.33 against target 7btf as well also has docking score is 7810 and free energy is -301.85 against target 3D0I. It shows that Di-O-(2-Thienoyl) curcumin has significant binding score as well greater free energy for the target 3D0I than the reference drug remdesivir for its target 7btf. That demonstrates this modified product also has powerful impact against Covid-19 pandemic along with assurance of druglikeness properties. Quercetin has docking score 3996 and free energy is -106.86 against target 7btf as well also has docking score 4492 and free energy -191.44 against target 3DOI. Quercetin a naturally occurring product found in several plant's edible fruits and vegetables is also a good preventive agent against Covid-19 pandemic with assurance of druglikeness properties. It shows that our daily basis food products also have potential to fight against Covid-19. Glabridin has docking score 4876 and free energy is -71.10 against target 7btf as well also has docking score is 5242 and free energy is -221.26 against target 3D0I. An anti-viral drug that could also acts against Covid-19 pandemic although it shows less druglikeness property. Glycyrrhizin has docking score 7924 and free energy is -218.32 against target 7btf as well as also has docking score is 8824 and free energy is -275.12 against target 3DOI. Glycyrrhizin a great candidate for treatment of corona virus infected patients. This anti-viral drug is significant candidate because having better docking score than referenced drug candidate for its target. Along with assertion of druglikeness properties it could be used as potential drug to treat corona virus infection.

V. CONCLUSION

All the drugs that have been selected as therapeutic option for the treatment of coronavirus infected patients have been evaluated through Lipinski's rule. All components are herbal products that are rare in causing its side effects so all of them could be a potential drug to treat corona virus infection widespread. All proposed therapeutic candidates are naturally available or have been found as one of the components of natural products. Curcumin and modified curcumin (Di-O-(2-Thienoyl) curcumin) are a kind of Indian spices which is food supplement. Both the candidates have good docking score with inhibitory effect on RNA dependent RNA polymerase enzyme along with ACE2 receptor protein present as a receptor for corona viruses in several human epithelial cells. Quercetin an important component of onion and garlic which is a type of vegetables is also have great potential to prevent corona virus infection by destroying effect of RNA dependent RNA polymerase enzyme as well as by interacting with ACE2 receptors. All above three candidates (curcumin, modified curcumin and quercetin) could be preventive measures against corona virus infection. Glabridin also has potency to bind with ACE2 receptor protein and inhibit internalization of corona virus inside human epithelial cells. Glycyrrhizin has great potential to bind with RNA dependent RNA polymerase enzyme as well as with ACE2 receptors. Glycyrrhizin even as good as remdesivir drug that has been approved by FDA for corona virus treatment because this anti-viral agent have docking score with RNA dependent RNA polymerase enzyme as well as with ACE2 receptors is greater than that approved drug remdesivir showing that this proposed anti-viral drug could be used for the treatment of corona virus infection.

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