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Artificial Intelligence Derived Artemisinin Drug Compound Acts as an Effective Candidate against SARS-CoV-2 Receptors: An In-Silico Study to Combat COVID-19

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Abstract

Background: Global outburst of coronavirus has challenged the whole world to discover drugs to combat the current pandemic. Repurposing drugs is a promising approach as it provides new openings to challenge the emerging COVID-19. However, in the epoch of big data, artificial intelligence (AI) technology offers to leverage computational methods for finding new candidate drugs through an In-silico approach.

Aim and Objectives: The aim and objectives of our present work basically are the designing of a plant-derived compound against the COVID-19 receptors which might act as effective therapy along with predicting the outcome of the disease with a deep learning program language that is python (anaconda) 2.7 version.

Methodology: Artificial Intelligence technology helps in understanding the interactions of coronavirus with receptors through the computer-aided drug designing process (CADD). The ligand-protein interactions were prepared with the Maestro (Schrödinger) program which aids to study the docking pose of artemisinin compound with SARS-CoV-2 receptors like 7CTT, a nonstructural protein (NSP) and 7MY3 Spike glycoprotein. Thus, Artificial Intelligence technology examines the drug-target interaction with Neural Networking built with a deep learning machine algorithm and predicts the outcome of the disease with python program language.

Results: Artemisinin exhibited the highest antiviral activity against the SARS-CoV-2 receptors like 7CTT and 7MY3. The three-dimensional structures of the ligands and SARS-CoV-2 receptors were retrieved from the PubChem Open Chemistry Database. The ligand-protein interactions were performed with the help of the Maestro (Schrödinger) program, which revealed MM/GBSA values of 7CTT interaction with derivative ligands of antimalarial compounds such as D95 (-45.424), artemisinin (-35.222), MPD (-31,021), MRD (-21.952) and 6FGC (-34.089), whereas with 7MY3 spike glycoprotein interactions MMGBSA values for D95 (-26.304), MPD(-18.658), MRD(-28.03) and 6FGC (-13.47) binding affinities have followed Lipinski rule of 5 and further predicted the outcome with random forest decision tree with an accuracy of about 75% with python program.

Conclusion: Repurposing of the drug through an In-silico approach against the SARS-CoV-2 virus revealed its antiviral actions. The docking studies approach has shown the XP score, gliding energy, and MMGBSA values which were predicted with a deep learning program built with Artificial Intelligence technology.

Keywords: Artemisinin, SARS-CoV-2, Lipinski rule, Protein-ligand interactions, Random Forest decision tree, Artificial Intelligence

1. Background

Coronavirus belongs to the viral family Coronaviridae which is mainly accountable for instigating pneumonia-like symptoms and hence regarded as a worldwide menace ever since its first outburst in 2002 (Jabeer Khan 2020). The variants of Severe Acute Respiratory Syndrome Disease (SARS), and Middle East Respiratory Syndrome (MERS) materialized in the years 2002 & 2013, correspondingly leading to elevated gastrointestinal and pulmonary dysfunction (Hilgenfeld and Peiris, 2013). Nevertheless, the third outbreak of SARS-COV-2 was in 2019 with symptoms ranging from the common cold to more severe acute respiratory failure (Kong WH. *et al.,* 2020). WHO (World Health Organization) has announced this malady as a pandemic and revealed that it continually spread the virus to more than 20 million populace (Worldometer, 2020). Nevertheless, it is currently acknowledged as the greatest materialization of communal health.

Literature reports from various studies have recognized the incubation periods for COVID-19 to be one week from day one of contact (Lauer *et al.,* 2020; Backer *et al.,* 2020). However, in accordance with China's Novel Coronavirus Pneumonia Diagnosis & Treatment Plan (Seventh Edition Trial) based on the signs and symptoms. Nevertheless, COVID-19 patients are classified into trivial, modest, severe, and critical based on their signs & symptoms. Nevertheless, several scientists are underway on a number of clinical trials such as cell therapy, antiviral therapy, immunotherapy, and the use of Chinese herbal medicine approved by the Food and Drug Administration (FDA) against COVID-19 (Jean *et al.,* 2020). Various, antiviral

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compounds such as lopinavir & ritonavir have not revealed antiviral efficacy in contrast to standard therapy (Guan 2020). The antimalarial agents such as chloroquine and hydroxychloroquine are confrontational. Nonetheless, limited clinical trials have revealed that hydroxychloroquine has failed to treat COVID-19 (Tang 2019). The National Institute of Health has counselled suspending the clinical trials involving hydroxychloroquine since it is harmless, and many reports displayed its ineffectiveness (National Institute of Health).

Naturally occurring substances found in phytomedicines have been shown to have therapeutic potential but differing mechanistic activities against SARS-CoVRSCoV-2 based on prior reports on their safety profiles (Huang *et al.,* 2020). The angiotensin-converting enzyme 2 (ACE2), heat shock protein A5 (HSPA5), and substrate-binding domain (SBD) of SARSCoV-2 are involved in the attachment of the virus to human cells, but Kumar *et al*., (2020) and Elfiky (2020) have demonstrated that natural products have the capacity to impair this attachment. Several other studies also demonstrated that the SARS-CoV-2 papain-like protease (PLpro) was inhibited by plant-based compounds obtained from various plant species, including ginger and Alpinia officinarum (Goswami *et al.,* 2020).

However, the idea of repurposing a medicine is widely used nowadays to identify the likely treatments for the current pandemic sickness.. It has acquired greater perceptiveness for the capability to recycle already existing drugs (Jin *et al.,* 2020; Kandeel and Al-Nazawi, 2020). In contrast, artificial intelligence algorithms built with machine learning plus big data are regarded as supporting tools for molecular level discern. The AI developments and latest advancements in all fields of science and engineering have grasped the attention of all researchers to study the interactions of plant-derived compounds with receptors which might produce very less side effects and prolong the life span of the human species for many years. However, entire drugs predicted by employing AI technology in drug discovery were found to be potential against coronavirus (Ho, 2020). Currently, artificial intelligence machinery has been exercised broadly for exploiting drug research contrary to COVID-19. Moreover, the Artificial Intelligence platform was ascertained to be more helpful for the recognition of potentially available drugs with inhibitory activities on human coronavirus (HCoV) by employing several learning datasets (Ke *et al.,* 2020). However, the organically available plant flora rich in Phyto-constituents offer a beneficial and influential source of chemical compounds indicating antiviral activity.

In order to expand vision on the mode of action of artesunate, the most potential malarial compound was examined by Yuyong Zhou *et al.,* (2021) and carried out a time-of addition assay in the A549-hACE2 in-vitro cell line. However, Cao *et al.,* (2020) investigated artemisinin, artesunate, and its derivatives for efficacy against SARS-CoV-2 on the A549-hACE2 cell line. Further studies on its interaction and the binding potential need to be evaluated before conducting clinical trials. Furthermore, chemical alteration of these structures, directed by computer-based docking simulations, might enhance their potentiality and selectivity (Chen *et al.,* 2018). Hence, our CADD study with help of the Artificial Intelligence technology approach is regarded as a boon to the present situation, where the whole world is facing the dreadfulness of the pandemic disease outburst. Although, vaccines are available at present naturally derived products are always effective in comparison to vaccines. Therefore, have adopted Graphical Neural Network into the bio-medical complex which assists the amalgamation of multimodal and composite relationships. Currently, GNN has revealed an immense assurance in predicting interactions (e.g., drug-drug adverse interactions, PPIs, & target-drug interactions) and in the detection of the latest molecules (Muhammad *et al.,* 2020). GNN can also promote the repurposing of drugs by characterizing the intricate interaction between drugs and maladies.

Thus, our work basically aims in the designing of the plant derived compound against the covid-19 receptors which acts as effective therapy along with predicting the outcome of the disease with a deep learning program language that is python (anaconda) 2.7 version. However, at present state, no accurate medicines are available which alarms the prospects of repurposing existing drugs which is effective. We have studied the docking pose of artemisinin compound with SARS-CoV-2 receptors like 7CTT, a non-structural protein (NSP), and 7MY3 Spike glycoprotein and predicted the outcome of the disease with python program language through a random forest decision tree approach to identify ideal and effective ligand-protein interactions which further support in future clinical trials investigation. Thus, AI-based tools helped to investigate the in-silico potentiality of the artemisinin compound against coronavirus.

2. Materials and Methods

2.1. Protein-ligand Structure preparation

For the preparation of protein-ligand Maestro11.1, Schrodinger in silico tool was utilized to examine the ligand-target interaction for current studies (Schrodinger, 2017). Nevertheless, two objectives were preferred for the study 1) 7CTT, a nonstructural protein (NSP) and 2) 7MY3 Spike glycoprotein both SARS- CoV-2 receptor-binding domain (RBD) interfacing with artemisinin compound and its derivatives.

2.2. Drug-target docking

The artemisinin and its derivatives were obtained from RCBS PDB Protein Data Bank (www.rcsb.org). All drug compounds and their derivatives were docked with 7CTT & 7MY3 SARSCoV-2 receptor using the Maestro 11.1 module of the Schrodinger software. The ligands were prepared using Protein Preparation Wizard using default settings followed by pH 7.4, whereas drug compounds and their derivatives such as D95, artemisinin, MPD, MRD, and 6FGC with a default setting of receptor grid box range of z were 25.754 and 270.701 and grid box range of x is 10. The interaction with protein-ligand and its glide scores were examined thoroughly. However, greater negative values propose a more encouraging drug-protein interaction. Therefore, compounds with a score of -2 or above were contemplated as better candidates for inhibiting SARS-CoV-2 (Shah *et al.,* 2020).

2.3. Data Analysis

Correlation between features of the dataset that is the interaction of drug compounds and their derivatives against SARS CoV-2 affords significant information about their features and the degree of influence they have over the target value. The heat map of Pearson Correlation between the ligands and proteins of the dataset is analyzed, which distinctively revealed a relatively stronger outcome.

2.4. Data Pre-processing

The dataset contains data columns with the Date, String, along with Numeric types. However, we have categorical variables provided in the dataset. Machine learning language involves all input data to be passed in the numeric form. The input data to be performed is label-encoded, and this assigns a unique number to each and every categorical value in the column.

3. Results

3.1. Investigation of Artemisinin compounds' interaction with SARS-CoV-2

On docking, Artemisinin and its derivative compounds displayed the greater antiviral activity against the SARS-CoV-2 receptors like 7CTT and 7MY3. However, the 3D structures of the ligands and SARS-CoV-2 receptors were obtained from the (https://www.rcsb.org/) protein data bank. The ligand-protein interactions were performed with help of Maestro (Schrödinger) program, which has shown XP GScore and MM/GBSA values of 7CTT interaction with derivative ligands of antimalarial compounds such as D95 (-6.911) (-45.424), artemisinin (Pubchem ID 159028) (-2.605), (-35.222), MPD (-5.088), (-31,021), MRD (-3.044) (-21.952) and 6FGC (-9.617) (-34.089), whereas with 7MY3 spike glycoprotein interactions MMGBSA values for D95 (-2.208) (-26.304), MPD (-2.59), (-18.658), MRD (-2.581), (-28.03) and 6FGC (-5.082), (-13.47) binding affinities has followed Lipinski rule of 5. (Table-1)

Table 1. Molecular docking parameters of Artemisinin Antimalarial drug compound and its derivatives against SARSCOV-2 receptors such as 7CTT (NSP) and 7MY3 (spike glycoprotein) with its binding affinities and following Lipinski rule of 5 with grid box range 10

S.No	Compound Name	Receptor	RMSD	XP Gscore	MM/GBSA	Lipinski rule of 5	Grid box z range	Grid box X range
1	D95	7CTT	0.006	-6.911	-45.424	0	25.754	10
2	Artemisinin		0.033	-2.605	-35.222	0		
3	MPD		0.001	-5.088	-31,021	0		
4	MRD		0.018	-3.044	-21.952	0		
5	6FGC		0.005	-9.617	-34.089	2		
6	D95	7MY3	0.006	-2.208	-26.304	0	270.701	10
7	MPD		0.001	-2.59	-18.658	0		
8	MRD		0.018	-2.581	-28.03	0		
9	6FGC		0.005	-5.082	-13.47	2		

Moreover, it is observed that the interaction of 7CTT which is a non-structural protein revealed notable interaction with artemisinin and its derivative D95 with (XP GScore and MM/GBSA values = (-2.605) (-35.222) & (-6.911) (-45.424)). Furthermore, in 7MY3 spike glycoprotein also revealed good interaction as shown in table-1 and displayed good binding interactions (as shown in figures 1&2).

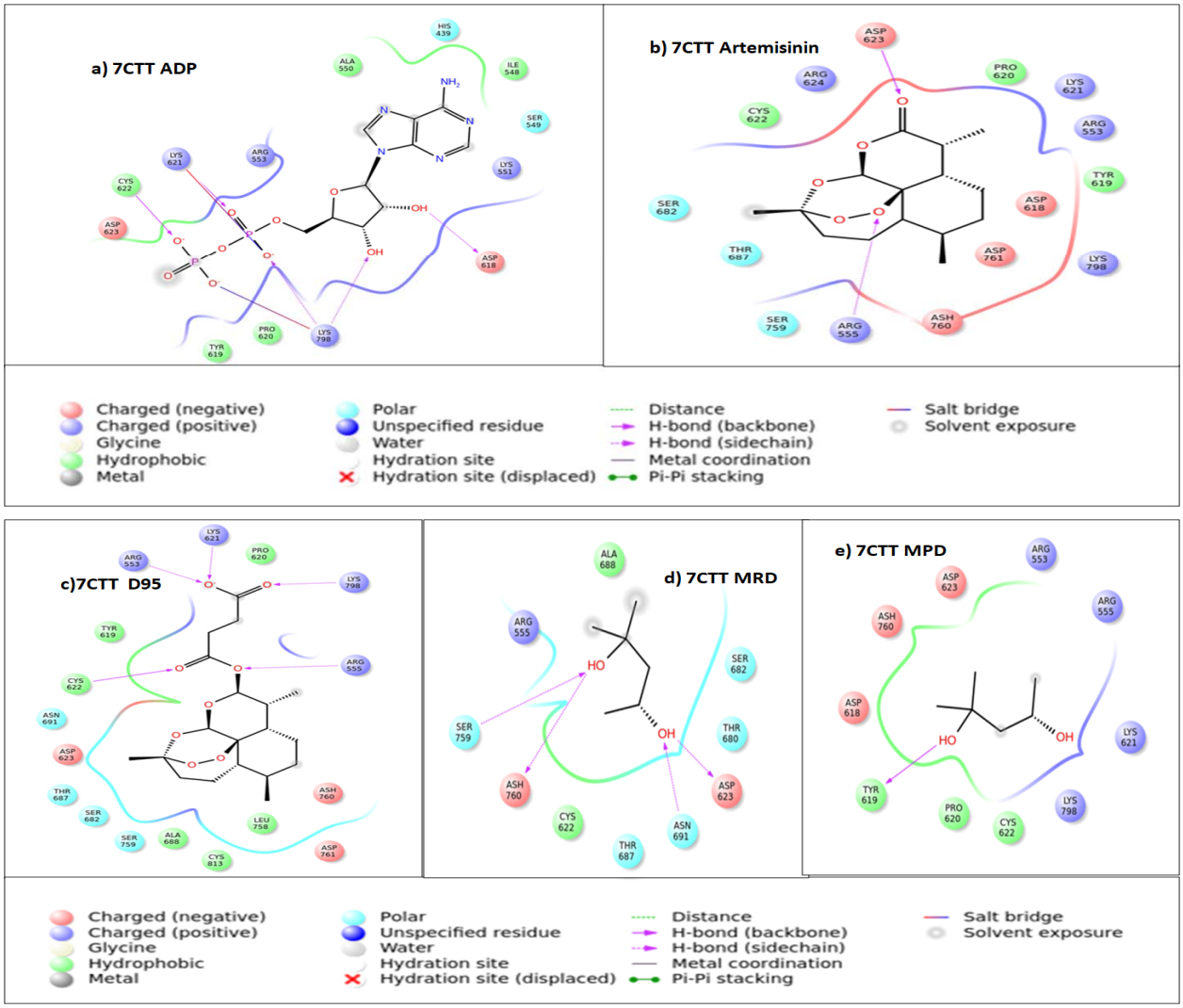

Figure-1A: 7CTT non-structural protein interacting with artemisinin and its derivatives and examined with ligplot+ a) Interaction of 7CTT with Adenosine-5'-Diphosphate, His-439, Lys-551, Asp-618, Cys-622, Lys-798,Arg-553,Tyr-619 and Pro-620. b) Interaction of 7CTT with Artemisinin residues that is Ser-682, Thr-687, Arg-555, Lys-551, Tyr-619 and Pro-620 c) Interaction of 7CTT with D95 residues such as Arg-553, Lys-798, Asp-623, Thr-687, Tyr-619 and Pro-620 d) 7CTT interaction with MRD, Asp-623, Thr-687,Arg-555, Cys-622 and Ala-688 e) 7CTT interaction with MPD, Lys-798, Arg-555,Asp-618,Cys-622, Tyr-619 and Pro-620. f) Docking of 7CTT with Artemisinin compound following Lipinski rule of 5.

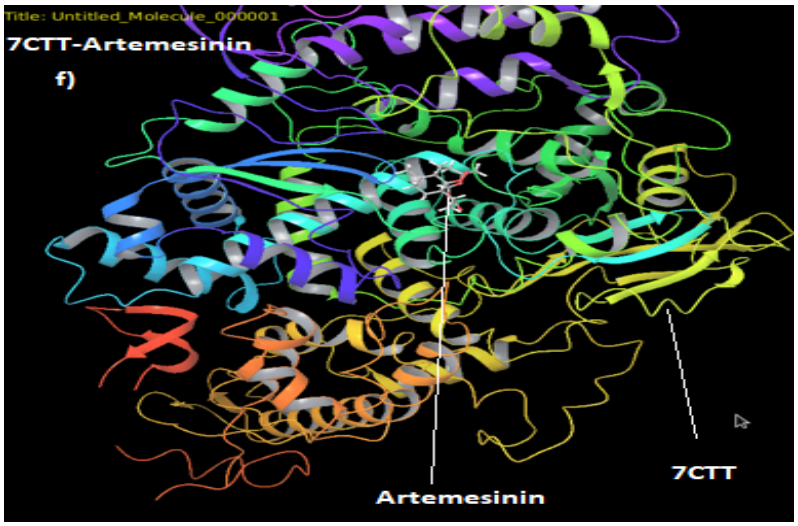

Figure-1B: 7CTT non-structural protein interacting with artemisinin is shown in this figure, and the interaction points are vision in ribbion structure.

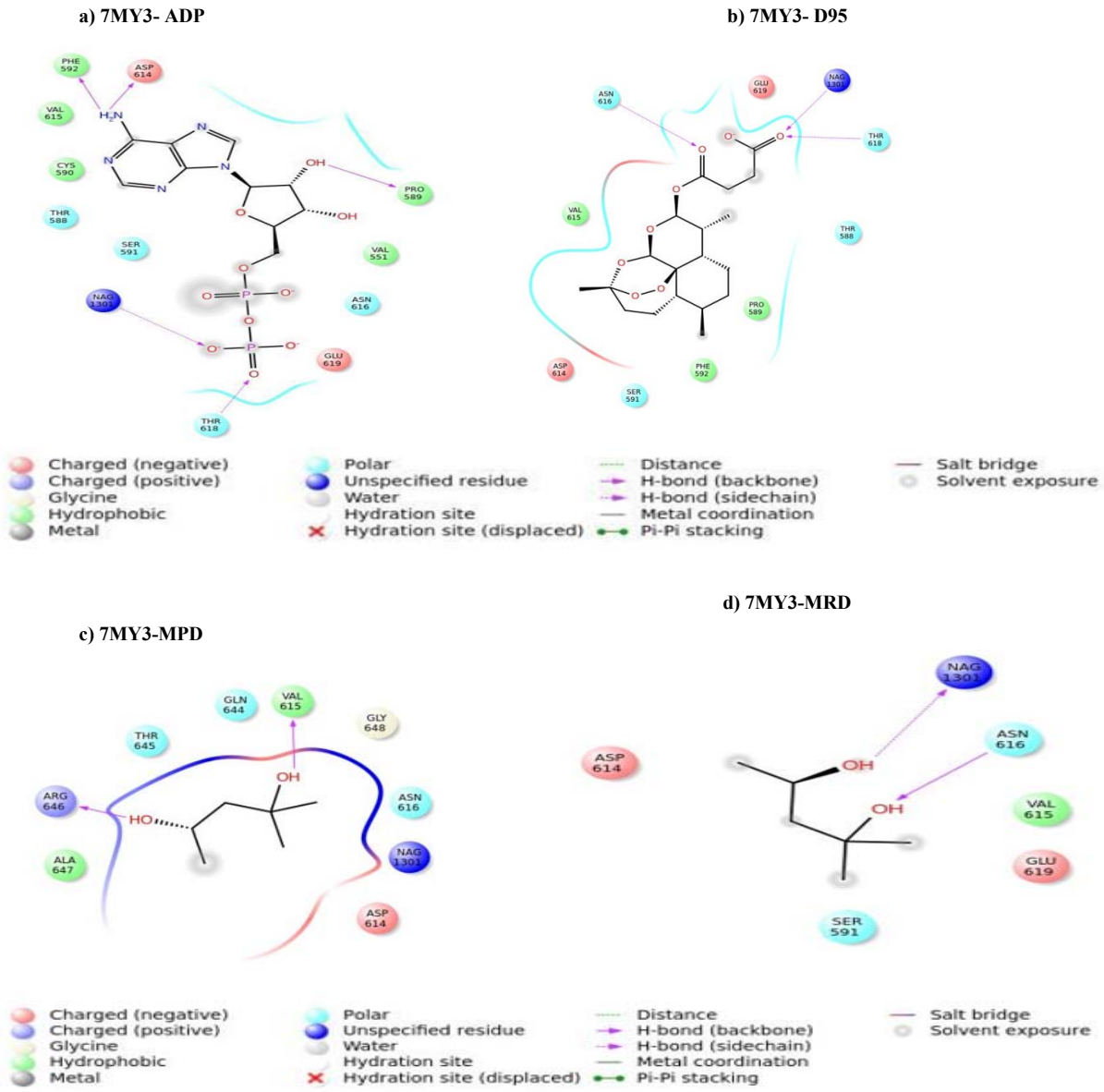

Figure 2: 7MY3 interaction with Artemisinin and its derivatives and examined with Ligplot+ a) Interaction of 7MY3 with Adenosine-5'-Diphosphate that is NAG-1301, Glu-619, Thr-618, Asn-616, Cys-590, Ser-591, Val-615, Phe-592, Pro-589 b) Interaction of 7MY3 with D95 NAG-1301, Asn-616, Val-615, Thr-618, Phe-592, Glu-619, and Pro-589 c) Interaction of 7MY3 with MPD residues such as NAG-1301, Arg-646, Gln-644, Asn-616, Thr-645, Val-615 and Ala-647 d) 7CTT interaction with MRD, NAG-1301, Asp-614, Ser-591,Glu-619, Val-615, and Asp-614.

3.2. Random Forest Decision Approach for predicting the outcome of docking interactions

RF (or Bagged DTs) is a machine learning approach that involves building multiple confusion matrixes via bootstrap aggregation. We have used two receptors of SARSCOV-2 to interact with the artemsinin and its derivatives compounds and predict its accuracy of binding. Furthermore, RF is utilized in remote sensing for predicting the accuracy/classification of data. The decision tree helps to improve the predictions. (Shown in Figure-3a &b).

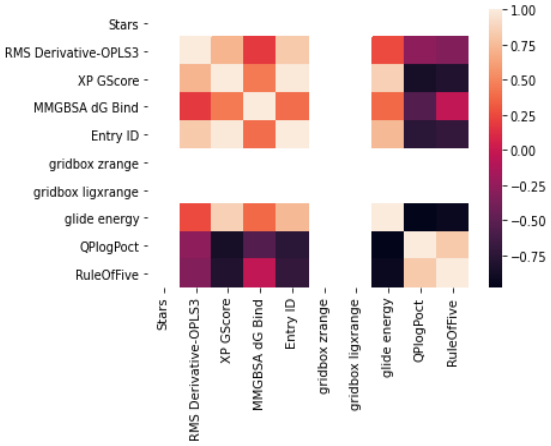

Figure-3a: Correlation between ligand protein interactions features

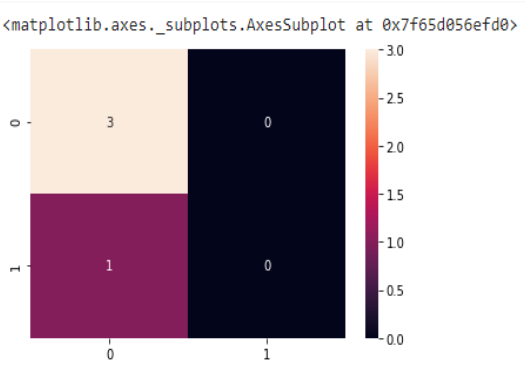

Figure-3b: Correlation matrix heatmap for the ligand-protein interactions

4. Discussion

SARS-CoV-2 was spread globally by the pandemic outbreak from December 2019 to the present (Hui *et al.,* 2020; Phan 2020), and COVID-19 is responsible for more than 3.9 million deaths (Huang, C. *et al.,* 2020; Paules 2020 and Lu *et al.,* 2020). This feverish, highly contagious respiratory systemic illness put many people's lives in danger. Remdesivir was given FDA approval as an antiviral drug for COVID-19 treatment. Additionally, new research have questioned its clinical effectiveness (Beigel, JH *et al.*,2020; Pan 2020; Dyer 2020). As a result, it was determined that using repurposed medications to treat the current pandemic outbreak was a successful method because the medications were already licensed for the treatment of other diseases. A. annua plant bioactive components with a lot of activity were used in the repurposed medications to treat malaria (Klayman 1985; Ferreira *et al.,* 2010). The primary active pharmaceutical ingredients (API) against COVID-19 showed better pharmacokinetic characteristics. The corona virus spread is regarded as an international problem globally. Currently, artificial intelligence has been utilized considerably for drug research against pandemic outbreaks. The employment of Artificial Intelligence is prominent for its intense potentiality for novel drug discovery (Coldeway, 2019; Segler *et al.,* 2018). The Artificial Intelligence platform has displayed significant inhibitory activity with contemporarily available drugs (Walters and Murcko, 2020). However, further study on artemisinin's interactions with two SARSCoV-2 receptors has been prompted in light of the antiviral efficacy of artemisinin and its derivatives in prior findings on herpes as well as on hepatitis B and C viruses (Ho *et al.,* 2014). But a number of studies have shown artemisinin's pharmacological qualities in addition to its additional mechanisms, such as its anti-inflammatory, anticancer, and antimalarial effects (Cao *et al.,* 2020; Kshirsagar & Rao, 2021). Artemisinin and its variants, among antimalarial drugs, were found to be effective against SARS-CoV-2. However, the docking of the artemisinin compound and its derivatives against two SARSCoV-2 receptors revealed the important functional groups and active residues with better G scores and **followed** Lipinski rule of 5.

Nonetheless, among the screened drugs (artemisinin, D95) against two SARS-CoV-2 receptors that is 7CTT & 7MY3, have shown better GScore values of -2.605, -6.911 in Table-1 displaying greater potent binding energy affinity. Docking pose of artemisinin and their derivatives investigated with Maestro Schrödinger Program on two receptors of SARSCOV-2, revealed significant functionally active residues Ser-682, Thr-687, Arg-555, Lys-551, Tyr-619, Pro-620 Glu-619, Thr-618, Asn-616, Cys-590, Ser-591, Val-615, Phe-592, Pro-589 as the best active binding sites with the MM/GBSA values of artemisinin, D95 -35.222 & 45.424 respectively.

The correlation matrix as a heat map with random forest decision tree predicted the accuracy of docking interactions of ligand-protein with an accuracy of 75%. Thus, our studies provide hypothetical evidence that utilization of artemisinin as repurposed drugs could potentially inhibit the binding of SARCOV-2 on ACE-2 receptor.

5. Conclusion

The current study showed that machine learning and deep learning programmes used to create artificial intelligence had a significant impact on the treatment of coronavirus. By preventing SARSCOV-2 from binding to two different types of SARSCOV-2 receptors, the artemisinin molecule and its derivatives were identified as an effective treatment candidate using an in-silico approach. The docking contacts' binding affinities and G scores adhered to the Lipinski rule of 5. Artificial intelligence technology is therefore viewed as a blessing and a useful tool for discovering repurposed medications that require clinical studies for validation.

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Competing interests

The authors declare that they have no competing interests1

Consent for publication

Not applicable.

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