INSILICO ANALYSIS OF EFFICACY OF REMDESIVIR, CHLOROQUINE, HYDROXY CHLOROQUINE AND 2DG ON COVID 19

PROJECT REPORT

Submitted by

J. ARUNDATHI	**114019342011**
B. SHIVA CHARAN	**114019342004**
K. SAIVARSHA	**114019572014**
B. BHANDAVI	**114019342002**
G. VARSHITA	**114019572010**

Under the supervision of

Dr. Y. Venkateswarlu

Asst. Prof of Biotechnology

GOVERNMENT DEGREE COLLEGE , KHAIRATABAD

Affiliated to Osmania University

Re-Accredited with ‘ B’ Grade by NAAC.

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Student Signatures:

1.

2.

3.

4.

5.

GOVERNMENT DEGREE COLLEGE,KHAIRATABAD

HYDERABAD

Affiliated to Osmania University

Re-Accredited with `**B**' Grade by NAAC

CERTIFICATE

This is to certify that

J. ARUNDATHI Roll No: 114019342011
B. SHIVA CHARAN Roll No: 114019342004
K. SAIVARSHA Roll No: 114019572014
B. BHANDAVI Roll No: 114019342002
G. VARSHITA Roll No: 114019572010

of Government Degree College, Khairatabad, Hyderabad submitted the Project Work on **"Insilico analysis of efficacy of Remdesivir, Chloroquine, Hydroxy chloroquine and 2DG on Covid 19"** to **JIGNASA STUDENT STUDY PROJECTS 2021-22**.

Supervisor **Head of the Department** **Principal**

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Statement of the problem or hypothesis

Pandemic diseases such as Covid 19 causes deaths of millions of people before development of drugs and vaccines, which usually require clinical trials on animals, which takes time 6 months to 2 years. Insilico analysis would help in determining the efficacy of the drugs in hours. Studying the drug efficacy within short duration is very much essential for life threatening viral diseases like SARS, Corona, etc. the second wave of Covid-19 in India was the "worst tragedy since the Partition (in 1947). Mortality rate increased by nearly 40 percent in the second wave (times of India). There is also shortage of beds availability in hospitals (Fig. 1).

Fig. 1. Covid 19 patients in hospitals

Highest mortality rate noticed during 2nd wave among the people with low immunity power, and comorbidity diseases (diabetes, hypertension and chronic kidney disease) and people with 70+ years (Fig. 2).

Fig. 2. Mass cremations during 2nd wave of Covid 19

Main reasons for this highest mortality rate is

1. Lack of vaccine,
2. Highest demand for Remdesivir
3. Fake drug market
4. Lack of awareness among the people about the effectiveness of the drugs available in the market.

Development of vaccine and further clinical trials is time taking. Govt. of India recommended several drugs as antiviral agents. Among these Remdesivir, chloroquine, Hydroxy chloroquine and 2DG (Fig. 3). Bioinformatics tools are available to screen the drugs and also to study the efficacy of the drugs on particular target. *Insilico* analysis of drugs efficacy on covid 19 would save time and cost and also controls the fake drug market. So the present study is computational study of these drugs to investigate their effectiveness against their target in COVID19.

Fig.3. Remdesivir, chloroquine, Hydroxy chloroquine and 2DG

Aims and Objectives

Aim

The aim is to screen available drugs on covid 19 using bioinformatics tools and techniques for their efficacy and safety

Objectives

1. To prepare the Covid-19 spike protein for docking studies
2. To identify the best drug among Remdesivir, Chloroquine, Hydroxy chloroquine and 2DG through molecular docking.
3. To study absorption, distribution, metabolism and excretion (ADME) properties of the drugs.

Review of Literature

A novel coronavirus, formally named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused coronavirus disease 2019 (COVID-19) worldwide, and it is the latest pandemic in the series of other infectious diseases including avian flu, Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). According to the World Health Organization, SARS-CoV-2 has caused an initial outbreak in Wuhan, China in the end of December 2019. Rapidly, it has become a global pandemic and spread to other countries such as Republic of Korea, Thailand, Iran, Italy, United States of America, India, etc., affecting more than 50 crore people with around 62 lakhs deaths worldwide (11th April 2022).

Last two decade much viral infectious disease emerged, such as Middle East respiratory syndrome-related coronavirus (MERS) and severe acute respiratory syndrome (SARS), still present a big concern to the world health. Recently a severe contagious viral infection was reported as it's started in China and transmitted to worldwide. The viral infection caused by a newly identified coronavirus, this virus was initially named as the 2019- novel coronavirus (2019-nCoV) on 12 January 2020 by World Health Organization (WHO). WHO officially named the disease as coronavirus disease 2019 (COVID19) and Coronavirus Study Group (CSG) of the International Committee proposed to name the new coronavirus as SARS-CoV-2, both issued on 11 February 2020 (Gavriatopoulou et al., 2020; Huang et al., 2020).

Since the beginning of the pandemic, several investigational drug options have been explored with limited success. Various health agencies across the globe have identified that social distancing, use of alcohol-based hand sanitizers, frequent hand washing with soap, and use of masks have been the most effective ways of preventing the transmission of the infection (WHO).

Structurally, Coronaviruses family is large, enveloped, single-stranded RNA viruses, where the virus is enclosed by a membrane that carries Spike protein (S) which will mediate the attachment step and entry into the host cell. Matrix (M) which involved in organizes the nucleoprotien inside, and Envelope (E) made up from lipid and protein and it is involved in the viral budding step and may be incorporated into the virion. Finally the Nucleocapsid (N) inside membrane that bounded the genomic RNA as showed in (Fig.4). An envelope-anchored spike protein guides coronavirus entry into host cells. It first attaches and bind with host Angiotensin-converting enzyme 2 (ACE2) receptor through viral S1subunit (found in viral surface spikes) and the fused the whole virus body into host membranes by aids of its S2 subunit.

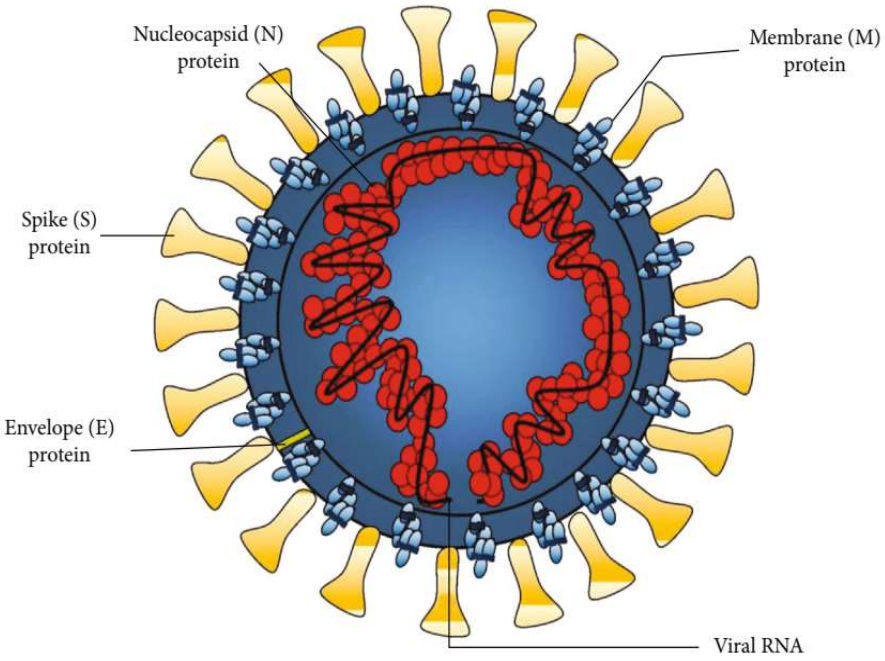

Fig.4. Structure of COVID 19 Virus

Similar to other coronaviruses, SARS-CoV-2 primarily infects the respiratory and gastrointestinal tract, with a cell tropism of nasal epithelial cells, pneumocytes, and alveolar macrophages in the lung and enterocytes in the bowel.25−27 Although not limited to only these specific cell types, evidence does support that cell binding via the viral S protein to the host receptor angiotensin-converting enzyme 2 (ACE2) is required for infection (Fig. 5) . Following entry of the virus into the host cell, the virus complex is then translocated to the endosome, where endosomal acid proteases cleave the S protein mediating membrane fusion (Letko et al 2020, Hoffmann et al 2020). The viral genome is released and translated into the viral replicase polyproteins PP1a and PP1ab, which are cleaved into functional proteins by viral proteases. Subgenomic templates for mRNA synthesis and translation of the viral structural proteins occur through discontinuous transcription.2 Viral genome replication is mediated by the viral replication complex, which includes

an RNA-dependent RNA polymerase (RdRp), helicase, exonucleaseN, and other accessory proteins. Subsequent assembly of viral nucleocapsids from the packaged viral genomes and translated viral structural proteins occurs at the endoplasmic reticulum-Golgi intermediate compartment,30 with infectious virions then released from the cell through exocytosis.

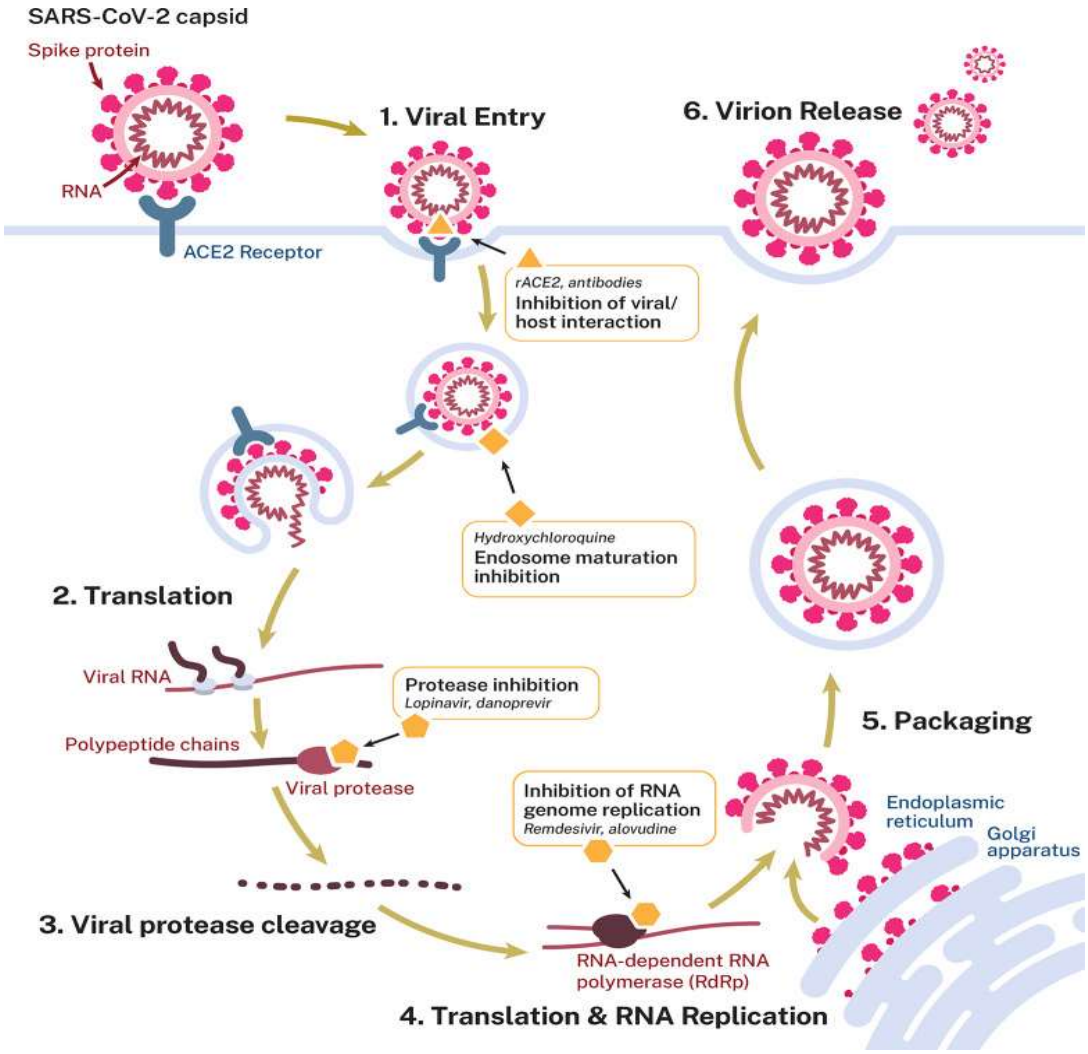

Fig. 5. Life cycle of SARS-CoV-2 in host cells (source: Eastman, et al (2020). ACS central science, 6(5), 672–683)

Mechanism of action of the drugs

Remdesivir

Remdesivir is the only FDA-approved drug for the treatment of COVID-19 patients. The active form of remdesivir acts as a nucleoside analog and inhibits the RNA-dependent RNA polymerase (RdRp) of coronaviruses including SARS-CoV-2. Remdesivir is incorporated by the RdRp into the growing RNA product and allows for addition of three more nucleotides before RNA synthesis stalls (Fig. 6 and Fig. 7).

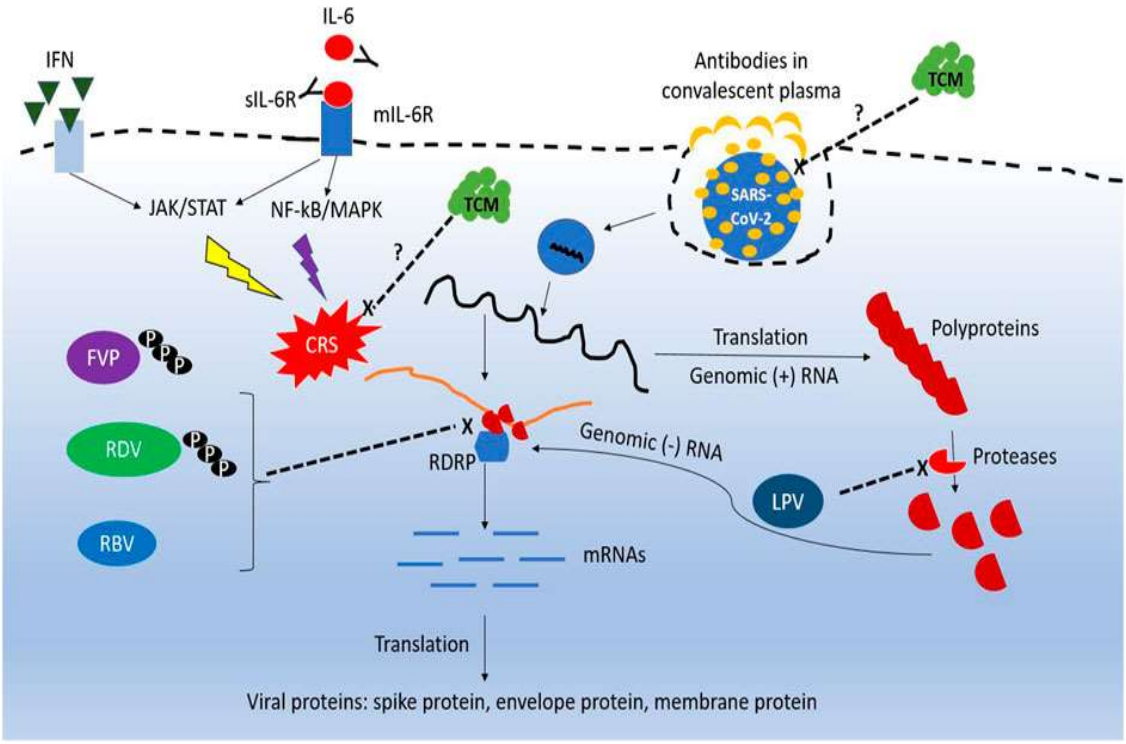

Fig. 6. Conceptual diagram of the mechanism for repurposing antiviral agents against SARS-CoV-2. RDV, remdesivir; FVP, favipiravir; RBV, ribavirin; IFN, interferon; sIL-6R, soluble IL-6 receptor; mIL-6R, membrane IL-6 receptor; TCM, traditional Chinese medicine.

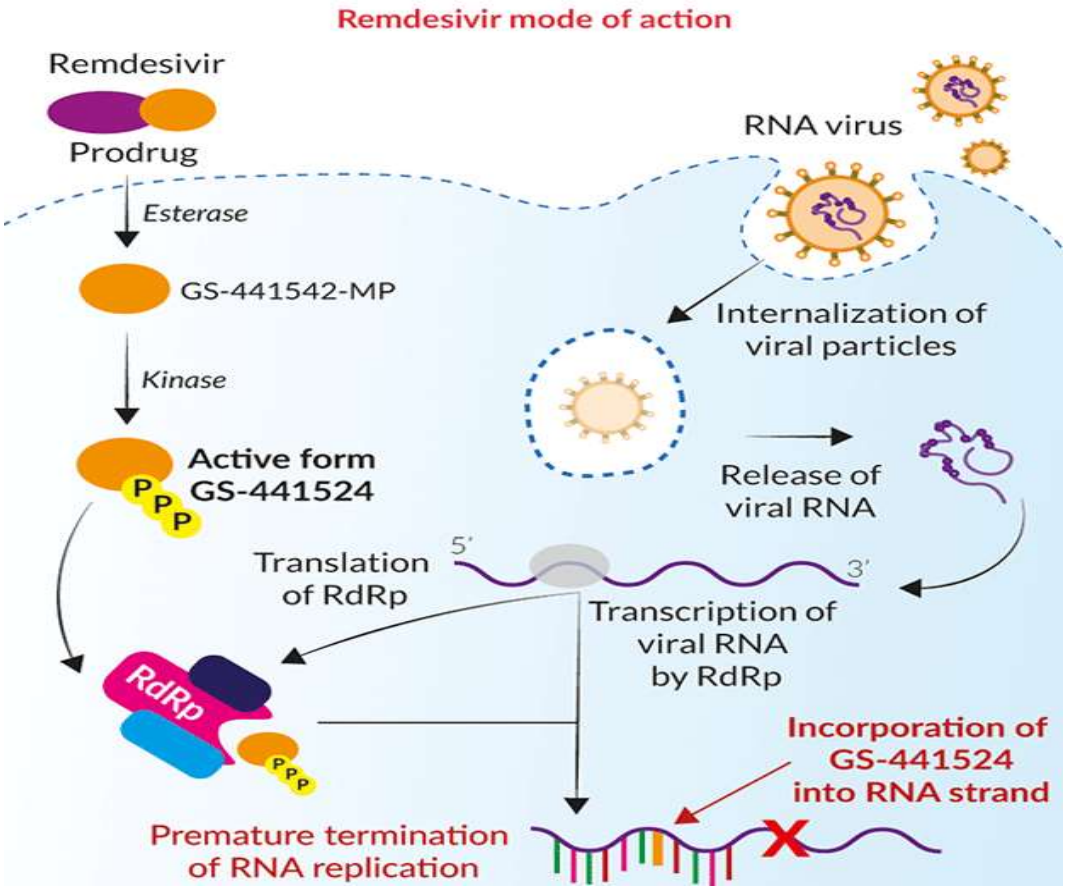

Fig. 7. Mechanism of action of Remdesivir

Remdesivir, also known as Veklury or GS-5734, is a 1'-cyano-substituted adenosine nucleotide analog prodrug that shows broad-spectrum antiviral activity. It was originally developed as an anti-viral against Ebola virus, but since has been shown to attenuate viral loads of a number of RNA viruses including respiratory syncytial virus (RSV) and β-coronaviruses such as SARS-CoV, MERS-CoV, and the causative agent of COVID-19, SARS-CoV-2.

Remdesivir specifically inhibits the activity of the viral RNA-dependent RNA-polymerase (RdRp), essential in viral replication. Upon entry into the cell, Remdesivir is rapidly metabolized into a nucleoside monophosphate (GS-441542 MP), which is then further processed into an active triphosphate form (GS-441524). GS-441524 is an adenosine triphosphate (ATP) analog and is thus, able to be used as a substrate by viral RdRp. GS-441524 outcompetes ATP for incorporation into the newly synthesized RNA strand, ultimately causing premature termination of the RNA product. However, unlike classic chain-terminators, the incorporation of GS-441524 causes delayed chain-termination downstream of this site (Tchesnokov, E.P. et al. 2019 and Agostini, M.L. et al. 2018). Importantly, it has been established that GS-441524 evades proofreading by the viral exoribonuclease (ExoN).

Remdesivir has been shown to have no significant inhibitory activity on human RNA Pol II and mitochondrial RNA polymerase (h-mtRNAP) . Recently, Remdesivir has been shown to exhibit protective effects in vitro against non-alcoholic fatty liver disease (NAFLD), by inhibiting pro-inflammatory signaling mediated by STING (Li, Y.N. & Su, Y. 2020).

Chloroquine (CQ), Hydroxy chloroquine (HCQ) mechanism of action

CQ obtained from the bark of Cinchona trees has been widely used for a long time as an antimalarial agent. In recent times, its hydroxyl derivative, HCQ, has proven to be safer than CQ due to the decreased renal and ocular toxicity and is being used as a substitute for CQ. CQ/HCQ has shown its potential to destroy SARS-CoV-2 in the following ways.

Inhibition Through Interference in the Endocytic Pathway

CQ inhibits fusion of lysosomes with autophagosomes due to dysregulation of syntaxin 17 (STX17) as shown in Fig. 8. Further, it hampers Golgi functioning and blocks transportation of material into lysosomes (Satarker et al 2020). HCQ also prevents the movement of SARS-CoV-2 from early endosomes to early lysosomes that are important for viral genome release as shown in Fig. 8. The rise in pH of lysosomes and endosomes mediated by HCQ further leads to formation of autophagosomes that break the S protein preventing the membrane fusion (Singh et al 2020).

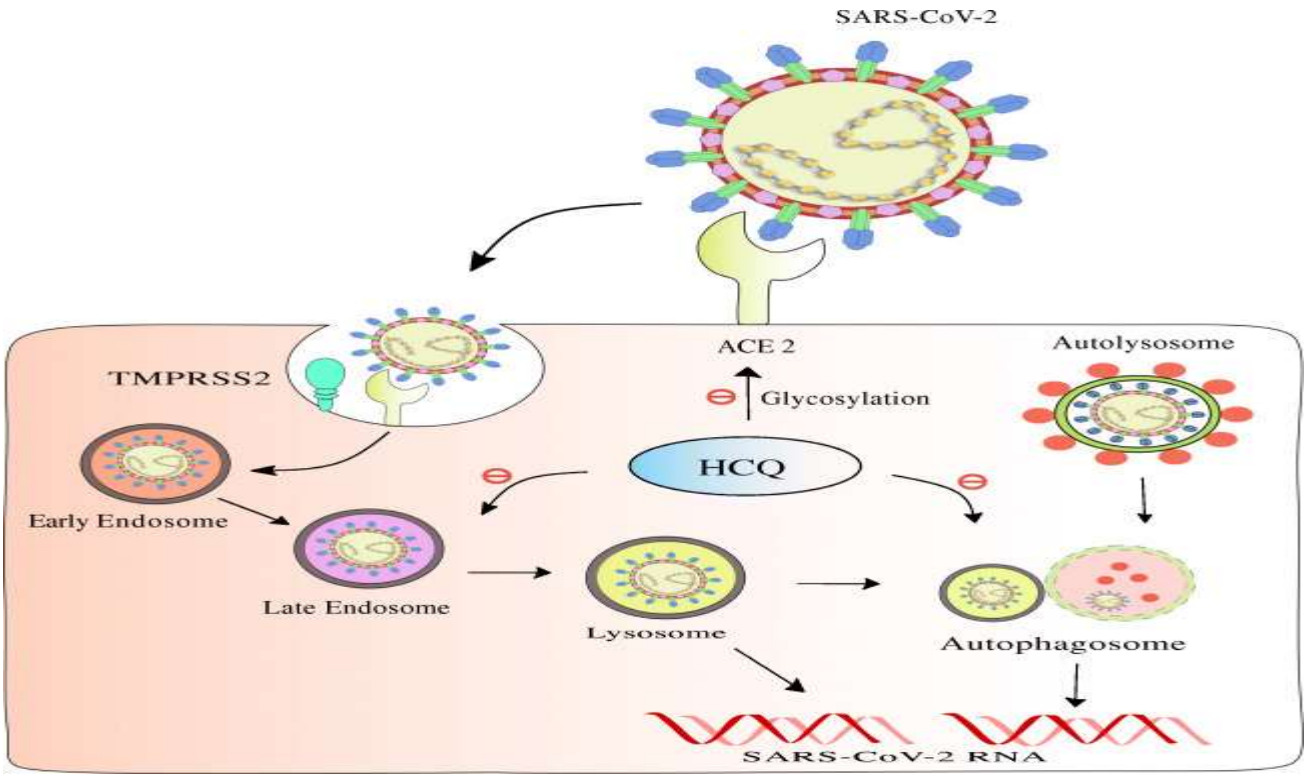

Fig. 8. The role of CQ/HCQ in inhibition of ACE2 glycosylation, conversion of early endosome into late endosome and formation of autophagosome

Inhibition Through Blockade of Sialic Acid Receptors

Recently, it has been identified that the N terminal of S protein in SARS-CoV-2 is similar to the region where sialic acid receptor binding occurs in MERS-CoV (Milanetti et al 2020). Therefore, SARS-CoV-2 may mediate its entry via these sialic acid receptors in the upper respiratory pathway and the previously known ACE2 receptor. Another study has also identified a novel binding site for the binding of gangliosides in the SARS-CoV-2 S protein N-terminal domain (NTD). Both CQ/HCQ were efficient in inhibiting the sialic acids, especialy the 9-O-SIA variant, however HCQ showed a better potency.

Mechanism of action of 2DG

2-deoxy-D-glucose (2-DG) has emerged as a polypharmacological agent for COVID-19 treatment due to its effects on the glycolytic pathway, anti-inflammatory action, and interaction with viral proteins. The following fig. 9 describes about the mechanism of action of 2DG.

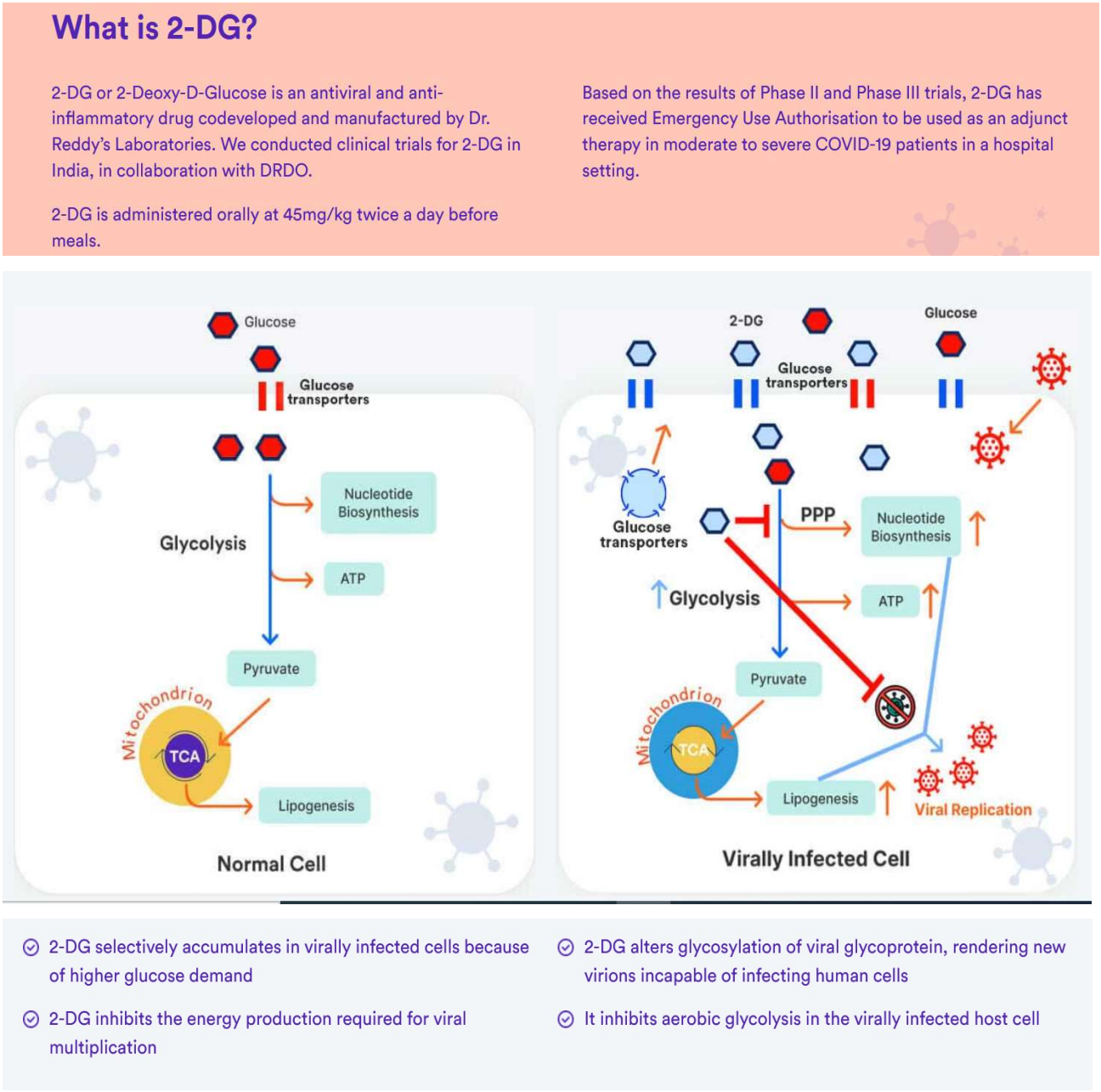

Fig. 9. Mechanism of action of 2DG on Covid 19.

Research Methodology

Preparation of SARS coronavirus spike receptor-binding domain

The three dimensional (3D) crystal structure of the spike receptor-binding domain of COVID 19 were obtained from Protein Data Bank server (2AJF accession No.) (http://www.rcsb.org/), with high resolution 2.9 A° created experimentally by X-Ray Diffraction method (https://www.rcsb.org/). Structure determination and visualization of the active site done by Discovery.Studio v2.5 software (Fig. 2). Covid-19 spike receptor-binding domain obtained from PDB databank (2AJF.pdb). This protein comprises of A, B, C, D, E and F chains. Water molecules

deleted from A, B, E and F protein by using Discovery studio visualizer. Chain A has protein groups and ligand groups and other chains deleted from structure for ligand docking. The final chain A is saved in PDB format after addition of Polar hydrogen atoms.

3D conformer of the four drugs

3D conformer of drugs is essential to dock the these drugs with Spike protein. 3D conformer of the four drugs Remdesivir, chloroquine, Hydroxy chloroquine and 2DG obtained from Pubchem data Bank in SDF format and their PubChem (https://pubchem.ncbi.nlm.nih.gov/) CID numbers are 121304016, 2719, 3652, 108223 respectively.

Docking of Drugs with spike protein using docking software

Docking software was used for the purpose of molecular screening of all the library of compounds by autodock wizard as the engine for molecular docking (Morris et al., 2008). The ligands were considered to be flexible during the docking period and the protein was considered to be rigid. Auto Grid engine was used for the generation of configuration file for the grid parameters. The Docking application was also used to predict/understand the amino acids residues present in the active site of the protein that interact with the ligands. The results less than 1.0A˚ in positional root-mean-square deviation (RMSD) were clustered together and considered ideal for identifying the favourable binding. The most negative (highest binding energy) was considered as the best candidate with maximum binding energy (Chandel et al., 2020; Rashmi et al., 2020).

Fig. Performing Docking studies with drugs

ADME analysis

The ADME properties (absorption, distribution, metabolism and excretion) of the selected compound were calculated using online Swiss ADME program (Diana et al., 2007). The major parameters for ADME associated properties includes Lipinski's rule of five (H bond acceptor, H bond donor, molecular weight, water/octanol partition coefficient), pharmacokinetic properties, the solubility of the drug, and drug likeliness were considered. The values of the observe properties are presented in Table 3.

Analysis of Data

The structure of Covid 19 spike protein prepared by deleting unwanted chains from total structure. Active site present in A chain. Hence rest of the chains deleted using Discovery Studio software. The chain A is used for docking studies of the four drugs (Fig. 10).

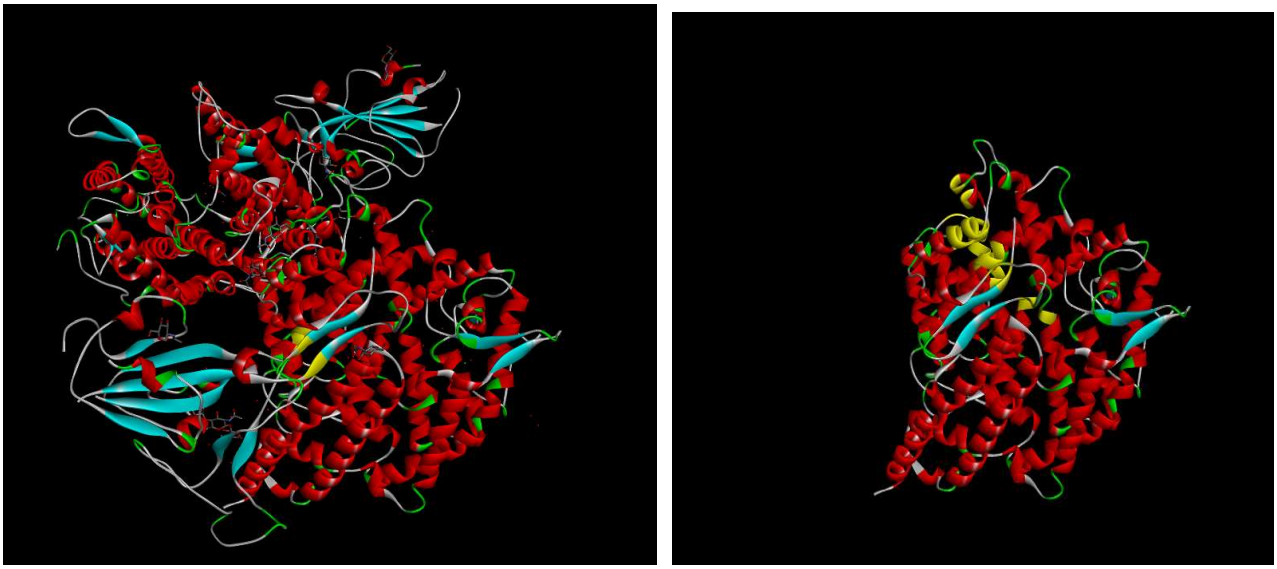

Fig. 10. 3D structure of total Spike protein of Covid 19. 3D structure Chain A of Spike protein of Covid 19

3D coformrs of the drugs downloaded from pubchem database and their structres are shown below Fig. 11. These 3D conformers are used for docking with spike protein chain A.

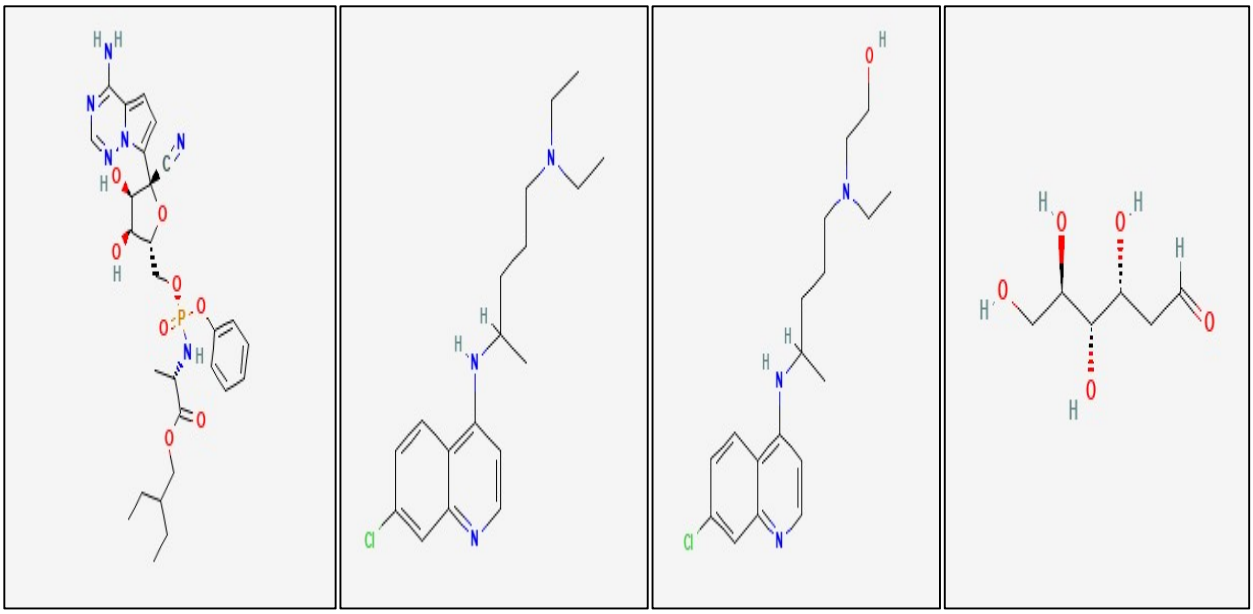

Figure 11: 2D Structure of Remdesivir, chloroquine, Hydroxy chloroquine and 2DG.

The chain A spike protein and 4 drugs Remdesivir, chloroquine, Hydroxy chloroquine and 2DG imported into the docking software. Grid box enlarged such that it covers the total protein during the docking program and it is shown in the following figure 12.

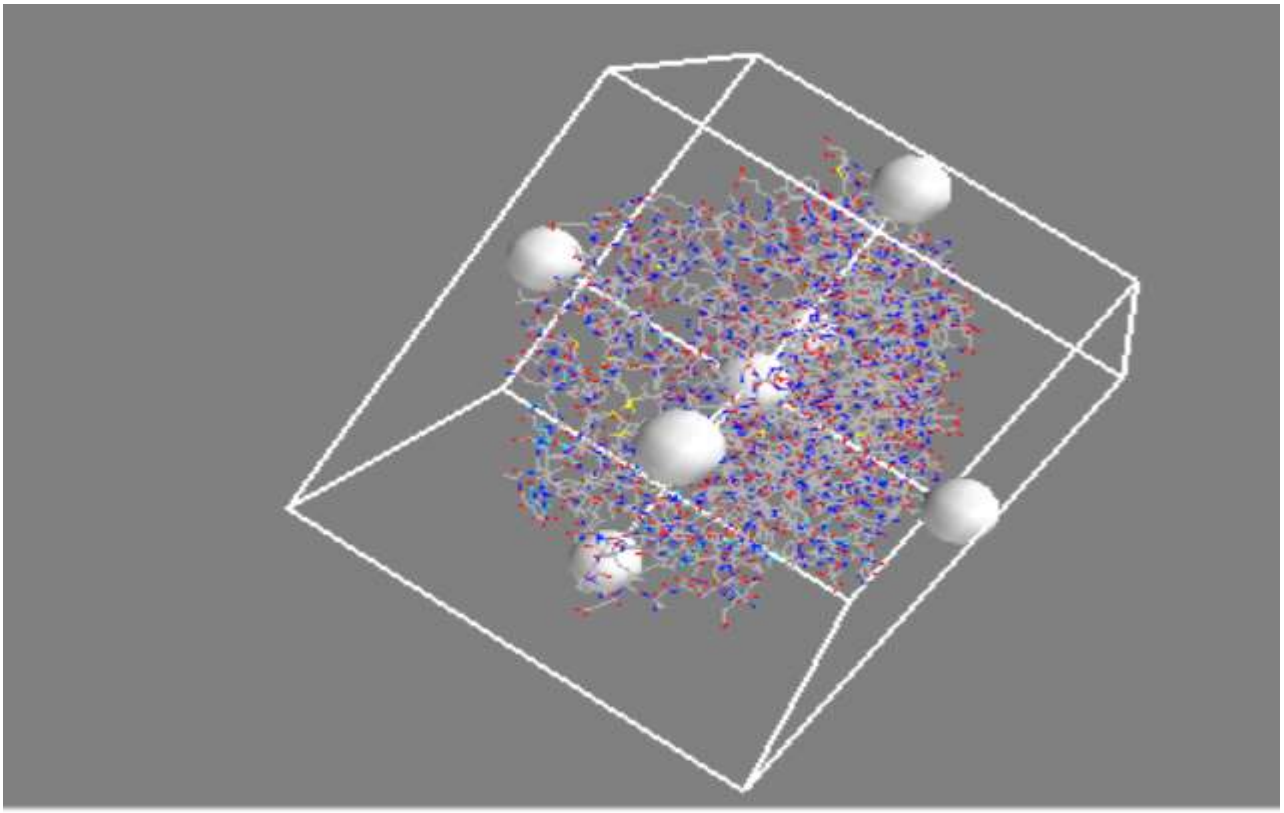

Fig. 12. Spike Protein with 4 drugs covered in grid box

Molecular Docking was performed to evaluate the effectiveness of four recommended drugs against COVID-19 spike protein, the binding free energy, full fitness and Gibbs energy (ΔG) are main functional score that reflects the affinity energy to bind process between the ligand- protein to form a complex, and which one that has the lowest affinity energy to bind means has high functional score and become more stable interaction and binding. The molecular docking results of four drugs with spike glycoprotein showed in (Fig.13.)

The molecular docking results showed that Remdesivir have pretty good potential affinity with ΔG score of -8.3 to bind with preferred active site of A1 subunit of spike receptor-binding domain of COVID19, where this binding is occupied the allosteric conformation of active site and led to block it and prevent the active site from bind with other substrate, all these events lead to loss the function of the enzyme and disruption the main process of the target protein. The Chloroquine and Hydroxychloroquine both showed the binding affinity of around -6.0, and the lowest functional score was 2DG with (-4.2 kcal/mol) (Fig. 13).

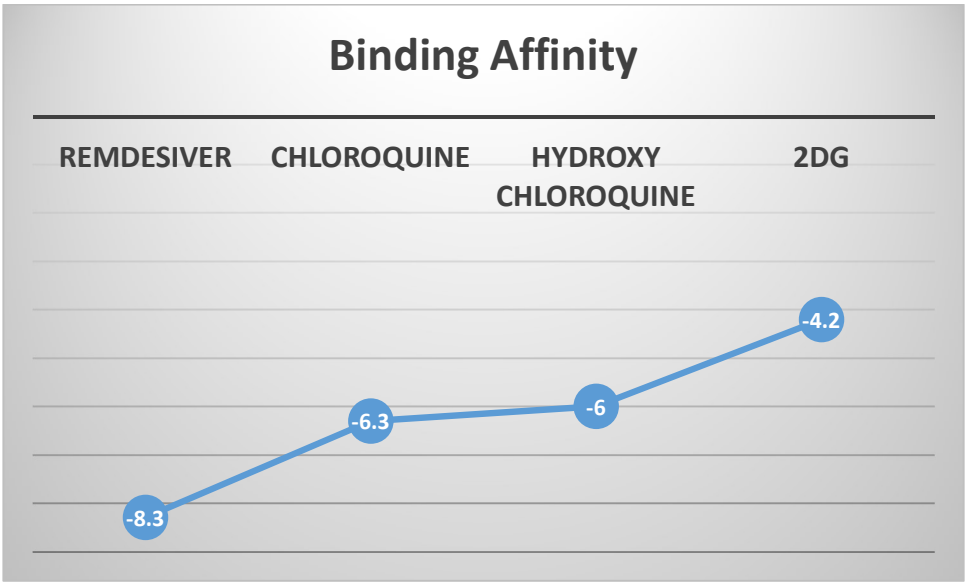

Figure 13: Molecular Docking Results of 4 Drugs Remdesivir, chloroquine, Hydroxy chloroquine and 2DG against A1 of spike receptor-binding domain.

The computational study showed a good indication can be seen by comparing the values of the binding free energy, full fitness, the Gibbs energy (ΔG), molecular weight and the amount of hydrogen interactions as standard inhibitor depending on Lipinski's rule of five. A bond forming can create a strong complex that characterized by a low binding energy, ΔG value, full fitness and the number hydrogen interactions with side chain of amino acid residues of active site of A1 subunit as

showed in (Fig. 14). Remdesivir with spike protein Receptor-Ligand interactions at molecular level showed in Figure 15.

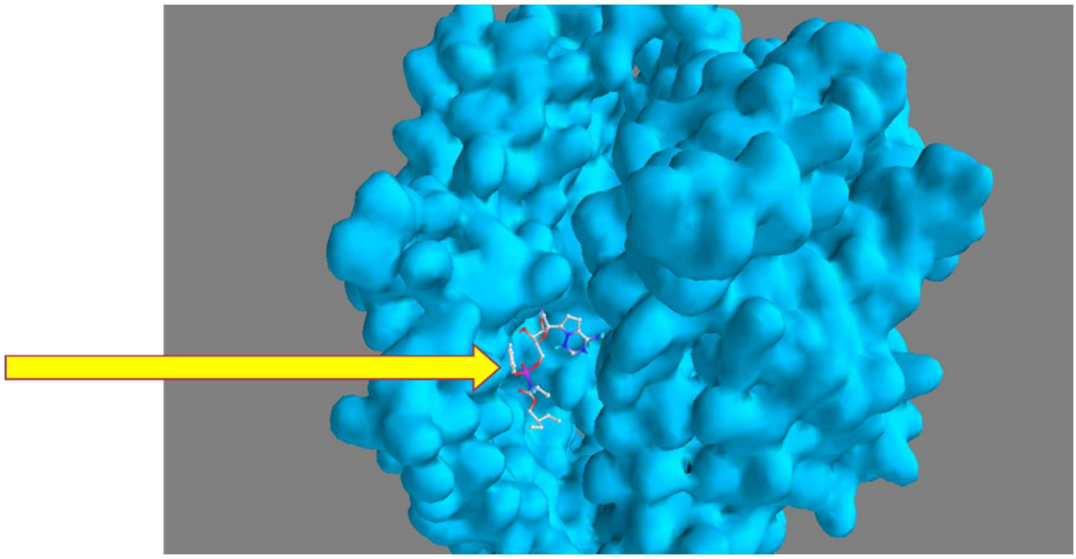

Figure 14: Remdesivir binding site at active site of A1 Subunit.

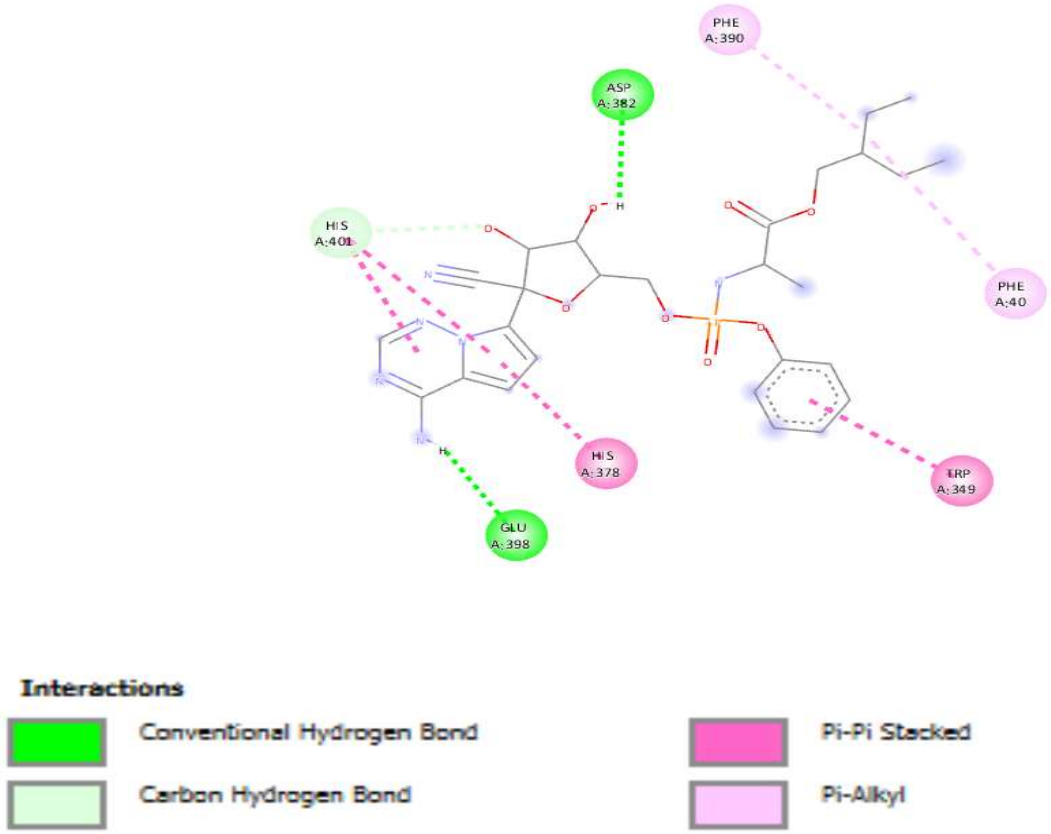

Fig. 15. Receptor-Ligand interactions at molecular level

ADME Properties of 4 drugs

Next, to get an insight about the drug-likeness properties of the lead compounds, all the 4 drugs were screened for ADME properties using swiss ADME programme and the results are shown in Table 3. The major criteria to understand the drug likeness properties of a particular compound involves Lipinski's rule of five (ROF) and if a specific lead compound with a certain pharmacological and biological activity has chemical and physical properties would make it a likely orally active drug in humans. Lipinski's rule of five
suggests the molecular properties which are critical in order to understand the drug's pharmacokinetics in the human body for example absorption, distribution, metabolism, and excretion (ADME).

An ideal drug following Lipinski's rule of five criteria are

(i) Molecular mass of a compound less than 500 Daltons,
(ii) No more than 5 hydrogen bond donors,
(iii) No more than 10 hydrogen bond acceptors,
(iv) Not more than 3 rotatable bonds
(v) An octanol-water partition coefficient log P not greater than 5.

Three or more than 3 violations of the Lipinski's rule do not fit into the criteria of drug likeliness and ideally it is not generally considered for further drug discovery. However, it is very important to mention that Lipinski's rule of five is not applicable to certain class of natural products and drugs which are substrates of
biological transporters such as antibodies and proteins and antibodies and are successfully FDA approved and widely distributed in the market. ADME propertied of 4 drugs showed in Table 1.

Table 1. ADME properties of selected drug molecules

S.No	Drug molecule		ADME properties Lipinki's rule or rule of five (ROF)					Drug likeliness
			Molecular weight (<500 Da)	H-bond donor (5)	H-bond acceptor (<10)	Rotatable bonds (<3)	Log P (<5)	
1	Remdesivir	Values	602	4	12	14	3.24	Yes
		Violation of Lipinki's rule	Yes	No	Yes	Yes	No	
2	Chloroquine	Values	320	1	2	8	3.95	Yes
		Violation of Lipinki's rule	No	No	No	Yes	No	
3	Hydroxy chloroquine	Values	335	2	3	9	3.2	Yes
		Violation of Lipinki's rule	No	No	No	Yes	No	
4	2DG	Values	164	4	5	5	0.52	Yes
		Violation of Lipinki's rule	No	No	No	No	No	

Findings

- The molecular docking results showed that Remdesivir have pretty good potential affinity with ΔG score of -8.3.
- 2DG is the safest drug according to the ADME properties.

Fig. Analysis of the data by the members of the project

Conclusions and Suggestions

The computational study showed that Remdesivir have potential candidate against COVID19, and other drugs showed low inhibition against same target. ADME studies 2DG is the safest drug of choice to treat patients with COVID19. Patients with good immunity power can recover from Covid 19 with 2DG. Remdesivir could be the last option for those people with high risk of comorbidity diseases. By duly following Covid 19 guidelines, increasing vaccination and right drug to right patient we can face Covid 4th wave with Omicron-XE variant with low death rates.

Outcomes to the society

1. Time saving

To study the efficacy of the drug in animals it takes 6 months to 2 years time. Insilico analysis would help in determining the efficacy of the drugs in hours. Studying the drug efficacy within short duration is very much essential for life threatening viral diseases like SARS, Corona, etc.

2. Right medicine to the Right patient – Controls Black marketing of drugs – Fake drugs control

During the Covid 19 pandemic second wave (March, April 2021) highest mortality cases of Covid 19 reported in India. One of the reason is acute shortage of Remdesivir. Patients who actually doesn't need Remdesivir injection also getting with their influence. The actual cost of Remdesivir injection is around Rs. 3000. Where as the price of Remdesivir in black market is more than 1.0 lakh rupees. Because of the demand for Remdesivir injection, fake drugs also manufactured several companies.

Lucknow police arrests gangs over black marketing of Remdesivir in UP

Police also seized cash from the youths who were in possession of the drug

By Puja Awasthi | Updated: April 23, 2021 16:20 IST

Lucknow Police seized Remdesivir vials which were to be sold in the black market; (right) Fake Remdesivir injection vials | Supplied

Patient families struggling to get Remdesivir

3. Ready to face Covid 4th wave with Omicron variant?

The Omicron variant of Covid 19 reported in December 2021. XE variant reported in 6th April 2022. The Govt. of India approved 2DG as one of the safest drug for treatment of Covid 19, when there is an acute shortage for Remdesivir. Patients with good

immunity power can recover from Covid 19 with 2DG. Remdesivir could be the last option for those people with high risk of comorbidity diseases. By duly following Covid 19 guidelines, increasing vaccination and right drug to right patient we can face Covid 4th wave with Omicron variant with low death rates.

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