RESEARCH ARTICLE

Hyaluronic Acid - 2-Deoxy-D-Glucose Conjugate Act as a Promising Targeted Drug Delivery Option for the Treatment of COVID-19

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ABSTRACT: In the present study, we propose Hyaluronic acid - 2-Deoxy-D-Glucose (HA-2DG) conjugate as a novel drug for the treatment of COVID-19. *In silico* molecular docking studies HA-2DG and 2-Deoxy-D-Glucose (2DG) against four different SARS-CoV-2 viral protein (Mpro, RdRp, PLpro and S protein) revealed that HA-2DG conjugate showed better binding affinity (-6.2, -7.2, -7.0 and 6.4 Kcal/mol) with all four screened SASR-CoV-2 viral targets than the antimetabolite drug 2DG alone (-4.8, -4.9, -4.6 and 4.7 Kcal/mol) respectively. ADMET analysis of 2DG and HA-2DG revealed that HA-2DG possessed reduced toxicity than 2DG alone. The study also revealed that the HA-2DG conjugate has multiple advantages of efficient drug delivery to its CD44 variant isoform receptors of the lower respiratory tract, highest interactive binding affinity with SARS-CoV-2 protein targets. Moreover, the HA-2DG drug conjugate possesses added advantages of good biodegradability, biocompatibility, no toxicity and non-immunogenicity. In conclusion, our study suggested that further *in-vitro* and *in-vivo* examination of HA-2DG drug conjugate will be useful to establish a promising early-stage antiviral drug for the novel treatment of COVID-19.

KEYWORDS: Hyaluronic acid, conjugation technology, 2-Deoxy glucose, COVID-19, targeted drug delivery

https://doi.org/10.29294/IJASE.7.4.2021.1995-2005

1. INTRODUCTION

COVID-19 is an infectious respiratory disease caused by SARS-CoV-2, a new zoonotic virus that undergoes mutational variability [1]. Since early 2020 the new respiratory syndrome COVID-19 has caused 3,575,895 deaths as of May 2021. The economic and social costs are unthinkable [2]. In an excellent article several antiviral drugs for the treatment of COVID-19 disease have been reviewed and mentioned that it was also effective in treating COVID-19 disease, in the present medical emergency conditions that the worldwide is facing [3-5].

More recently *2-Deoxyglucose* (2DG), has also been shown to inhibit SARS-CoV-2 virus replication. There is currently no approved therapy for COVID-19, India is in the grip of a devastating second wave of the disease, with more than 24 million cases and 338,000 deaths, India is now the epicenter of the global pandemic. On 17th May 2021, the Indian Government after the emergency approval rolled out the new local *2-Deoxyglucose* (2-DG) drug for the treatment of COVID-19 [6], originally designed for the treatment of cancer, because it positively and effectively to inhibited SARS-CoV-2; the government released the drug to be used as an adjunct therapy in moderate to severe cases. It also pointed out that due to its simple makeup; it can be easily produced and made available in plenty in the country, raising hopes that it can eventually be widely used and ease the current COVID emergency. A large number of patients are facing severe oxygen dependency and need hospitalization; the drug is expected to save precious lives due to its mechanism of operation in infected cells. However, some critics are warning that there is not enough data available to back up the drug's emergency approval as a COVID-19 treatment.

The original work on the use of 2-Deoxy-D-

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Received: 19.04.2021 **Accepted:** 25.05.2021 **Published on**: 31.05.2021

glucose (2DG) for the treatment of cancer has thrown light on how the drug works, it has shown to compete with the glucose metabolism in cancer cells that depletes cancer cells of the energy it needs to survive and replicate that finally leads the malignant tumour cells to die. This finding that 2-DG inhibits glycolysis due to the formation and intracellular accumulation of 2-deoxy-D-glucose-6-phosphate (2-DG6P), inhibiting the function of hexokinase and glucose-6-phosphate isomerase, inducing malignant cell death led to its potential therapeutic use for the treatment COVID-19. In addition to glycolysis inhibition, other molecular processes are also affected by 2-DG [7].

As an analogue of glucose, uptake of 2-DG into cells occurs through glucose transporters (GLUT1). After the drug 2-DG is phosphorylated at the C-6 position to 2-DG-6- Phosphate**.** But, unlike glucose-6P, 2DG-6P cannot be further metabolized by glucose-6P isomerase (GPI) and is "trapped" in cells due to limited dephosphorylation by phosphatases, inhibiting subsequent steps of glycolysis [8]. The patients with epilepsy cardiac toxicity were encountered at preclinical study in rats, that during research on a potential anticonvulsant and disease-modifying agent for it induced reversible cardiac toxicity in rat [9].

Small molecule drugs such as antitumor and in the present case 2-Deoxyglucose (2-DG) compounds have recently been conjugated to synthetic and natural polymers; the advantages envisaged in this strategy are reduced toxicity, increased solubility and stability, localization and controlled release of the drug The 2-DG has been conjugate with platinum (II) complexes for glucose transporter 1 (GLUT1) mediated anticancer drug delivery have been synthesized and evaluated for in vitro cytotoxicity study with seven human cancer cell lines; the results revealed that 2-DG conjugated platinum (II) complexes are GLUT1 transportable substrates and exhibit improved cytotoxicity in cancer cell lines that over express GLUT1 when compared to the clinical drug, oxaliplatin; the study revealed the potential of the 2-DG conjugated platinum (II) complexes as lead compounds for further pharmaceutical investigation [10].

Our proposal to use hyaluronic acid for the targeted delivery of 2-DG is based on its versatile biological roles it plays in our body. Hyaluronan also known as hyaluronic acid (HA) is a naturally occurring polysaccharide of a linear repeating disaccharide unit consisting of β-(1→4)-linked D-glucopyranuronic acid and β-(1→3)-linked 2-acetamido-2-deoxy-D-glucopyranose, which is present in extracellular matrices, the synovial fluid of joints, and scaffolding that comprises cartilage. Despite the simplistic structure of hyaluronan, it behaves quite differently from other glycosaminoglycans in its mechanism of synthesis, its size, its physicochemical properties such as the network-forming, viscoelasticity, and its charge characteristics, important to many biochemical properties of living tissues. It mediates its biological functions through specific protein receptors present on the different cell surfaces, which include CD44 [11], HARE [12], RHAMM [13], and LYVE [14].

HA has been widely used by the biomedical community as a starting material for the fabrication of hydrogel matrices, tissue engineering tools, drug delivery vehicles or drug depot systems, and tissue filler or surgical devices [15-17]. HA-based materials may impart biological activity to cells, as evidenced by changes in cellular behavior, due to the cells' ability to interact with biomaterials based on HA compared to synthetic polymers, such as poly(ethylene glycol) (PEG). For example, the ability of HA to maintain stem cells in an undifferentiated state [18] and the involvement of HA-interacting proteins in tumor metastasis in HA gels [19] have been investigated. In drug delivery, the ability of HA to bind cell surface receptors has been explored for drug targeting purposes [20]. The biological functions of HA depend on the molecular size of HA, the HA binding proteins, its spatial and temporal distribution in tissues, and the cellular background and tissue stages. Mounting evidence confirms the involvement of HA in morphogenesis and wound healing, and its role in cancer progression and metastasis.

A dicarboxylic acid hemiester or hemiamide group with pharmacologically active compounds and with hyaluronic acid or with a hyaluronic acid ester, has been used for the preparation and a controlled release of medicament containing those derivatives have been described. The advantage of using HA, substituted by a spacer arm, with compounds with anti-inflammatory activity, is represented by the possibility of having a slow release of the drug and of obtaining a synergistic effect of the two components, after hydrolysis of the bond. Indeed, both hyaluronic acid and steroid-type anti-inflammatory drugs (such as methylprednisolone) have proved to be efficacious in reducing symptoms associated with osteoarthritis of the knee. Similarly, HA-cholesterol, HA-propofol has been prepared to result in a number of drugs for the treatment of diseases such as cancer, arthritis, osteoporosis [21].

A number of anti-cancer drugs such as Camptothecin and Methotrexate have been conjugated at the C-6 position of the glucosamine moiety of the hyaluronic acid [22,23]. Hyaluronic acid is not only interesting because of its biocompatibility, bio absorbability and in the

transportation of the drug through the body but also because of its own therapeutic efficacy. For example, high molecular weight hyaluronan inhibits cell differentiation and promotes cell proliferation, being involved in tissue regeneration, wound healing, epithelial integrity and embryogenesis. Lower molecular weights HA are anti-angiogenic, immunosuppressive and hamper the differentiation by limiting the cell-cell interactions or ligand access to cell receptors [24-26].

Our objective of the present study is to propose a novel and efficient drug for COVID-19 disease, using tumor anti-metabolite drug, 2-Deoxy-D-glucose (2DG), covalently linking it at a specific position with the Hyaluronic acid (HA) to afford HA-2DG conjugate to increase its bioavailability, safe, improve its localization, controlled release in the body, enhance its overall efficiency, and eliminate or reduce systemic toxicity if any. The conjugation of 2DG to hyaluronic acid can be accomplished through the 2DG primary C-6 hydroxyl group to the hyaluronic acid C5′carboxylic group of the glucuronic moiety *via* an ester linkage for example, using succinic anhydride (21). In this scenario, the binding mechanism of 2-DG and HA-2DG with the said viral virulence factors will be assessed by means of *in silico* molecular docking simulations against four different SARS-CoV-2 target proteins, an efficient drug target for the treatment of COVID-19.

2. MATERIALS AND METHODS

2.1. Ligand generation

The 2D structure of 2-Deoxy-D-Glucose (2DG) and Hyaluronic Acid-2-Deoxy-D-Glucose (HA-2DG) was drawn with the help of ACD chemsketch [27]. Retrieved 2D Mol file format of 2DG and HA-2DG was submitted to "Online SMILES convertor and Structure file generator [28] and converted into 3D SDF format.

2.2.ADMET Calculation

Pharmacokinetic properties of 2DG and HA-2DG was screened by pkCSM is a web-based application to determine pharmacological efficiency of the drug candidate. pkCSM predicts the various parameters associated with ADME and toxicity behavior of various clinical compounds.

2.3. Preparation of Receptor and its Binding Site

Novel corona viral (SARS COV-2 or COVID-19) Proteases (Mpro and PLpro), Spike protein, and RNA dependent RNA viruses are the key viral molecules involved in the attachment, replication and reproduction of viral particle in the human host cells. These protein target molecules served as a novel target to inhibit the viral life cycle in human host cells. 3D crystal structures of SARS COV-2 main proteases Mpro (6LU7), papain like protease PLpro (6W9C), spike protein (6WPT), RNA dependent RNA polymerase (6M71) was retrieved from RCSB PDB database (https://www.rcsb.org/) [29].

2.4. Molecular docking

Autodock Vina (version 4) was employed for the present study and the calculations were carried out by Autodock tools [30]. Totally four viral targets proteins (Mpro, RdRp, PLpro and S protein) from SARS-CoV-2 and two ligands (2DG and HA2DG) were taken for our present study. Grid map for docking of protein binding pocket was calculated using Autogrid. The optimal grid size for x, y and z points of dimension were set for all the viral protein targets. Other parameters of docking such as docking assessment (~ 100 times), population size (150), energy evaluation (maximum number 250,000) generations (maximum number 27,000), rate of mutations (0.02), rate of cross-over (0.8) and other parameters of docking were set to default values using the autotor utility of the autodock tool. Docking results pose and 2D interaction plot of the viral target protein with ligand was analyzed using receptor-ligand interaction options in Discovery Studio visualizer v2.5.

3. RESULT AND DISCUSSION

3.1. ADMET Calculation

ADMET for 2DG and HA-2DG calculated using pkCSM web based application. ADMET results revealed that the 2DG and HA-2DG molecule processes very good pharmacokinetic properties such as absorption, bioavailability, distribution, excretion and toxicity parameters which are tabulated and presented in Table 1. The molecule 2DG and HA-2DG show similar ADMET but some absorption, distribution and toxicity properties improved upon conjugation. In absorption Caco-2 cell permeability HA-2DG shows -0.725 than 2DG -0.405 10^6 cm/sec value. Similarly in distribution HA-2DG shows the highest CNS and BBB values -6.873 and -2.253 than its free form 2DG shows -4.37 and -1.107 respectively. Oral Rat acute toxicity LD50 value of HA-2DG shows 2.656mol/kg values than 2DG 1.053mol/kg indicating that toxicity value of 2DG drug is declined upon hyaluronic acid conjugation. Excretion of 2DG found that the total clearance of 0.901ml/min/kg. Both 2DG and HA-2DG shows no inhibition of

against five different drug-metabolizing enzymes. They also show that nil toxicity in the case of HERG, AMES and hepatotoxicity.

It is quite interesting to mention that our previous research study [31] results revealed that HA-HCQ conjugate shown more bioavailability, less toxicity and ease of clearance from the body when compared to its free form of drug HCQ. It is worth mentioning here that conjugation of drugs with hyaluronic acid enhances the pharmacokinetic profiles of the drugs themselves. In the drug discovery process the ADMET properties of the compounds have an important role to play as these properties are mostly accountable for failure of drugs in approximately 60% of the clinical trials cases and our previous *In silico* virtual drug screening studies for COVID-19 confirm that both anti-viral molecules from both natural and synthetic drugs show good agreement with the above statements [32-35].

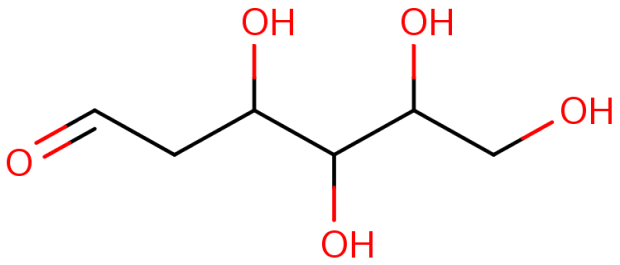


Fig.1 Structure of 2-Deoxyglucose (2DG)

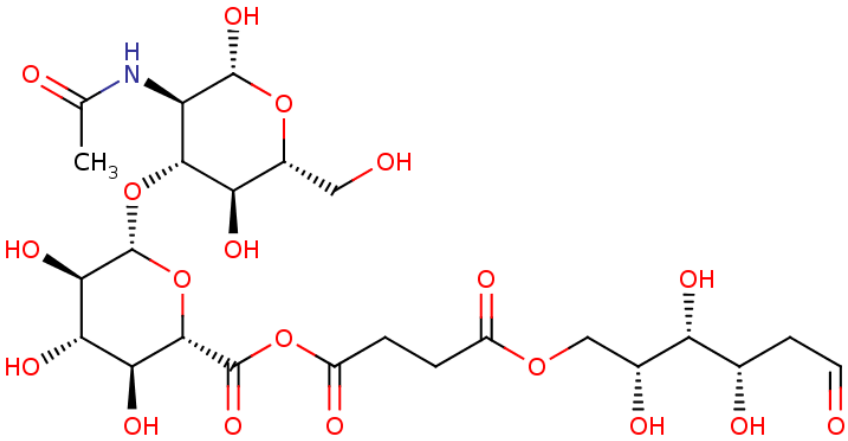


Fig.2 Structure of Hyaluronic Acid- 2-Deoxyglucose conjugate (HA-2DG)

3.2. Docking Study

Four Different COVID-19 target proteins (Mpro, PLpro, RdRp and Spike protein) and their docking score and 3D pose with 2DG and HA-2DG is reported in Table 2 and their detailed molecular interaction between them is tabulated and presented in Table 3 & Figure 3-10.

The results of the molecular docking study by Autodock Vina software between COVID-19 viral targets and 2DG and HA-2DG exhibit the binding affinity and docking score ranging from -4.8 Kcal/mol to -7.2Kcal/mol. HA-2DG exhibit the highest binding affinity -6.2Kcal/mol COVID-19 main protease (PDB ID 6LU7) essential for replication and reproduction of SARS COV-2, whereas 2DG shows hydrogen bonded interaction with Gly143,Ser144 residues of Mpro with the docking score of -4.2Kcal/mol. Corona Viral Mpro residues such as His41, Tyr54, Leu141, Asn142, Gly143, Cys145, His164, Glu166, Gln189 form hydrogen bonded interaction with HA-2DG. Whereas 2-DG forms two hydrogen-bonded interactions with Gly143, Ser144 residues of Mpro target.

HA-2DG exhibits binding affinity of -7.2Kcal/mol with COVID-19 viral RNA Dependent RNA polymerase (6M71), Papain like Protease (6W9C),

Spike glycoprotein (6WPT) respectively. Molecular interaction between COVID-19 viral spike glycoprotein with HA-2DG form hydrogen bonded interaction with Glu214, Tyr251, Lys254, Thr259 residues and form non bonded interaction with Lys306 residues of COVID-19 spike glycol protein with docking score of -6.4Kcal/mol. Whereas 2DG shows interaction with Tyr83, Ala131, Arg138, Glu143, Asn146 residues of spike glycoprotein with the docking score of -4.7Kcal/mol.

Molecular interaction between COVID-19 viral RNA dependent RNA polymerase with HA-2DG form hydrogen bonded interaction with Lys47, Tyr129, His133, Ser709, Asn781 residues and form non bonded interaction with Asp135,Asn138residues of COVID-19 spike glycoprotein. Whereas 2DG shows Asp761, Glu811, Cys813, Ser814 hydrogen bonded interactions with RdRp residues with the docking score of -4.9Kcal/mol.

Table 1 – ADME (T) properties of 2-Deoxy-D-Glucose and HA-2DG

ADMET PROPERTIES	2DG	HA-2DG
ABSORPTION		
Caco-2 cell permeability (10^6 cm/sec)	-0.405	-0.725
P-glycoprotein I Inhibitor	No	No
P-glycoprotein I Inhibitor	No	No
DISTRIBUTION		
CNS Permeability	-4.37	-6.873
Blood-brain barrier penetration (log BB)	-1.107	-2.253
METABOLISM		
CYP1A2 Inhibition	No	No
CYP2C9 Inhibition	No	No
CYP2C19 Inhibition	No	No
CYP2D6 Inhibition	No	No
CYP3A4 Inhibition	No	No
EXCRETION		
Total Clearance (log ml/min/kg)	0.901	1.704
Renal OCT2 Substrate (log mg/kg/day)	No	No
TOXICITY		
AMES Toxicity	No	No
hERG I & II Toxicity	No	No
Oral Rat Acute Toxicity (LD50) (mol/kg)	1.053	2.656
Hepatotoxicity	No	No
Skin Sensitization	No	No

Table 2: Docking Score 2DG and HA-2DG against SARS-CoV-2 Protein targets

Compounds	Docking Score (-Kcal/mol)			
	Mpro (PDB ID 6LU7)	RdRp (PDB ID 6M71)	PLpro (PDB ID 6W9C)	Spike Protein (PDB ID 6WPT)
2DG	-4.8	-4.9	-4.6	-4.7
HA-2DG	**-6.2**	**-7.2**	**-7.0**	**-6.4**

Table 3: Docking Score and Molecular Interactions of 2DG and HA-2DG against SARS-CoV-2 Protein targets

Docking Complex	Residues involved in bonded interactions	Residues involved in non-bonded interactions	Docking Score (-Kcal/mol)
Mpro-2DG	Gly143,Ser144	-	-4.8
Mpro-HA 2DG	His41,Tyr54,Leu141,Asn142,Gly143,Cys145, His164,Glu166,Gln189	-	-6.2
RdRp-2DG	Asp761,Glu811,Cys813,Ser814	Trp617, Trp800	-4.9
RdRp-HA 2DG	Lys47,Tyr129,His133,Ser709, Asn781	Asp135,Asn138	-7.2
PLpro-2DG	Ser212,Tyr213,Glu214,Tyr251,Thr257,Tyr305	Lys254	-4.6
PLpro-HA 2DG	Tyr213,Glu214,Lys217,Tyr305,Lys306,Lys254	Thr257	-7.0
Spike Protein-2DG	Tyr83,Ala131,Arg138,Glu143,Asn146	Tyr71	-4.7
Spike Protein-HA 2DG	Glu214,Tyr251,Lys254,Thr259	Lys306	-6.4

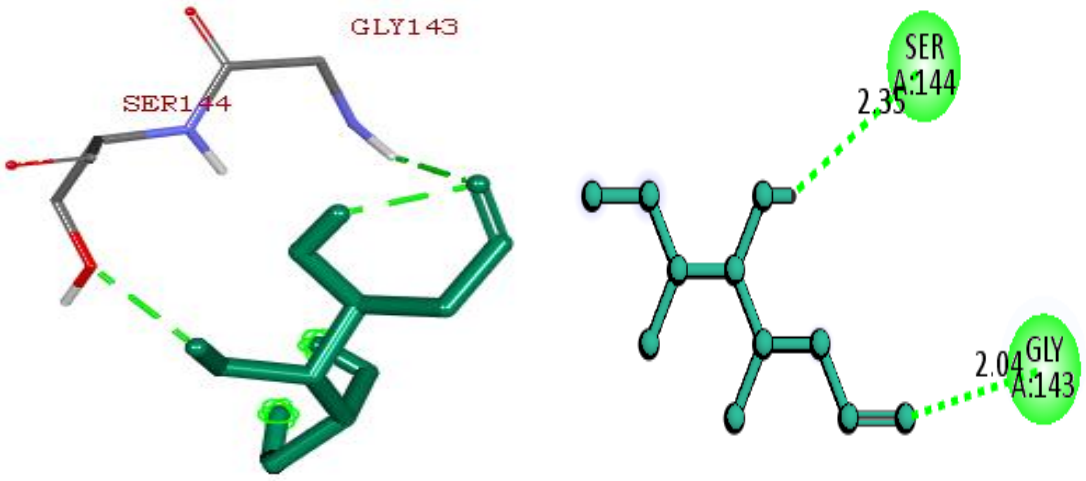


Fig.3. Mpro (PDB ID 6LU7)- 2DG Docking Complex 3D pose and 2D Interaction plot (-4.8Kcal/mol)

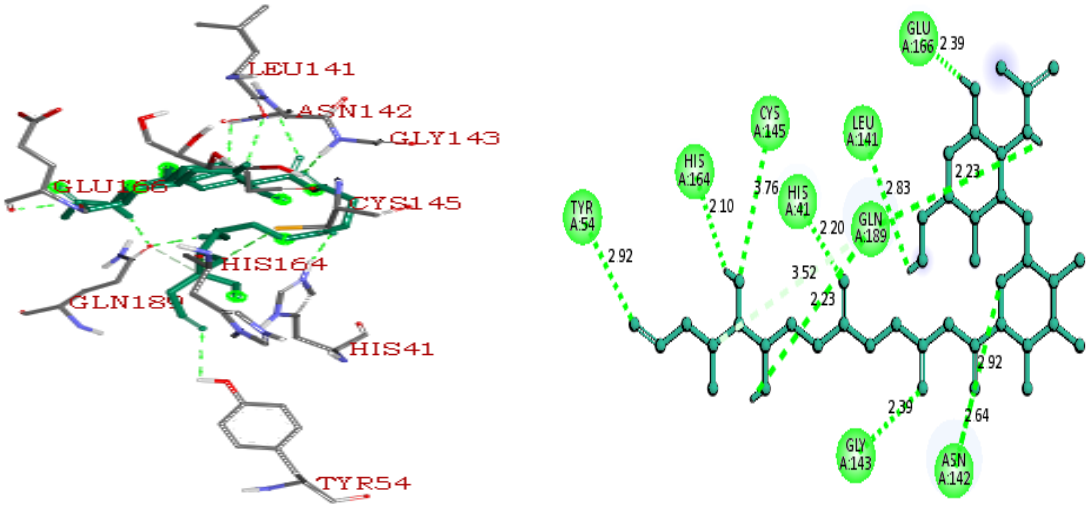
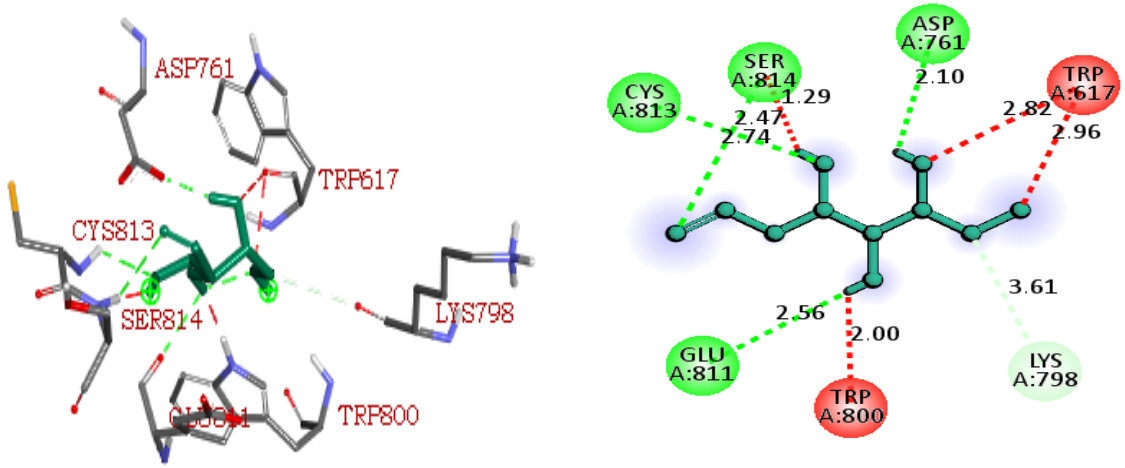


Fig.4. Mpro (PDB ID 6LU7)- HA 2DG Docking Complex 3D pose and 2D Interaction plot (-6.2Kcal/mol)



6.2Kcal/mol)

Fig.5. RdRp(PDB ID 6M71)- l;'2DG Docking Complex 3D pose and 2D Interaction plot(-4.9Kcal/mol)

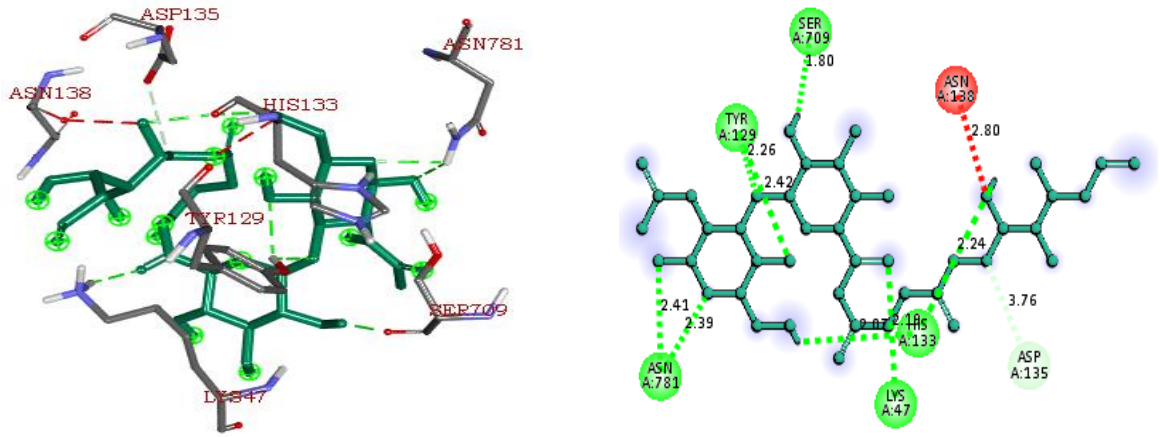


Fig.6. RdRp (PDB ID 6M71)- HA 2DG Docking Complex 3D pose and 2D Interaction plot (-7.2Kcal/mol)

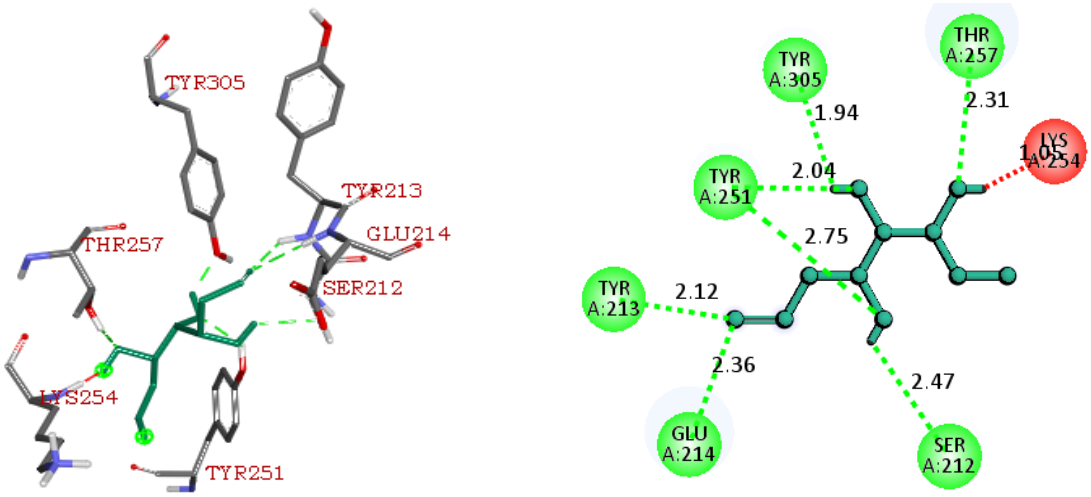


Fig.7.PLpro (PDB ID 6W9C)- 2DG Docking Complex 3D pose and 2D Interaction plot (-4.6Kcal/mol)

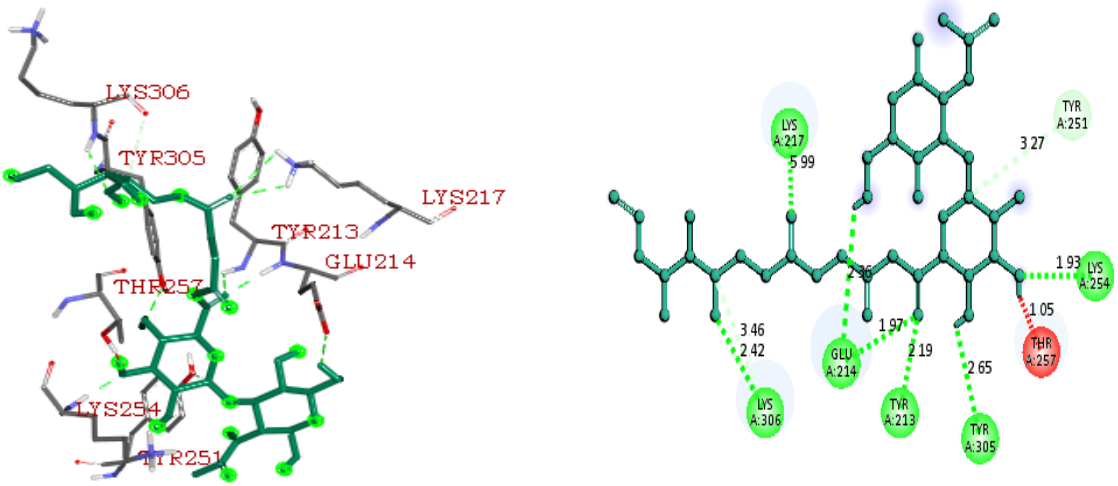


Fig.8. PLpro (PDB ID 6W9C)- HA 2DG Docking Complex 3D pose and 2D Interaction plot (-7.0Kcal/mol)

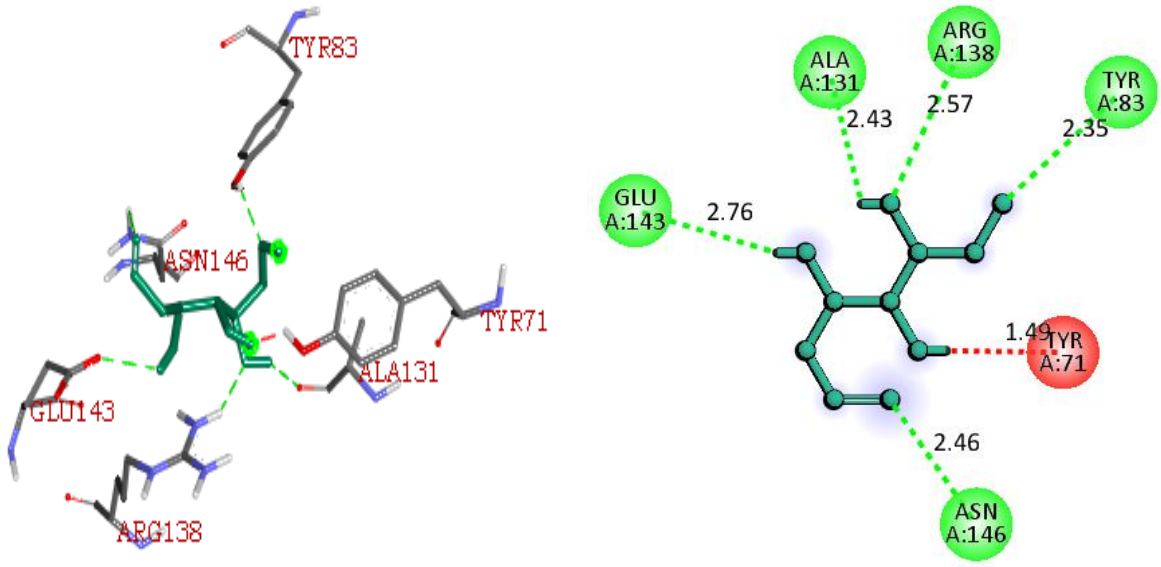


Fig.9. Spike Protein (PDB ID 6WPT)- 2DG Docking Complex 3D pose and 2D Interaction plot (-4.7Kcal/mol)

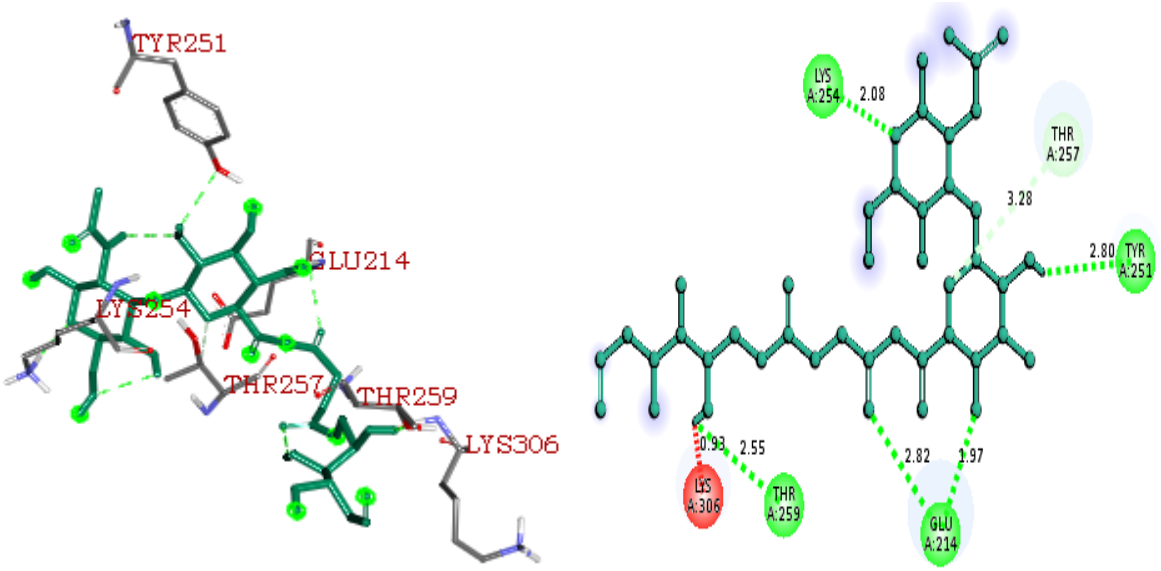


Fig.10. Spike Protein (PDB ID 6WPT)- HA 2DG Docking Complex 3D pose and 2D Interaction plot (-6.4Kcal/mol)

2DG is a glucose anti-metabolite that can effectively interfere with several glucose cellular pathways such as glycolysis, glycosylation, endoplasmic stress response (ER), phagocytosis and apoptosis. 2DG can inhibit glucose transport and glycolysis pathway by competitive uptake of 2DG competes with glucose. Competitive uptake of 2-DG leads to the obstructing energy-yielding pathways such as glycolysis [36]; inactivating the glycolytic enzymes; inducing cell cycle arrest and ultimately leading to inactivation of nCoV-19 in infected cells [37,38]. The depletion of ATP levels leads to activation of AMP-activated protein kinase (AMPK) which leads to the expression of p53 which ultimately promotes cell cycle arrest in the G1 phase in virus infected cells. All these factors would eventually cause a sensitized response that causes virus-infected cell death through apoptotic mechanism [39].

Recent *in-silico* docking study reveals that binding efficiency of 2-DG towards Mpro (E value -140.05 Kcal/mol) and viral endoribonuclease (E value = -168.65 Kcal/mol) has been found to be exceedingly better than that of antiviral drugs such

as Lopinavir and Favipiravir. Such significant binding affinity of 2-DG with that of SARS-CoV-2 viral receptors presumably indicates the probable mechanism of action of 2-deoxy-D-glucose as viral protease and endoribonuclease inhibitor. Viral protease is fundamental for continuing the viral life cycle of SARS-CoV-2 as it is required by the virus to catalyze the cleavage of viral polyprotein precursors which are ultimately necessary for viral capsid formation and enzyme production. Henceforth, the 2-deoxy-D-glucose moiety contingently inactivates the viral protease, thereby inhibiting the process of viral capsid formation. Furthermore, 2-DG may also be responsible for withholding the action of viral endoribonuclease, thereby halting the process of viral replication altogether [40].

2-Deoxy-D-glucose–induced cardiac toxicity was reproduced in a rat model demonstrating the association of elevated levels of NT-proBNP and BNP (NT-proBNP being more sensitive) with microscopic findings in the heart (myocardial vacuolar degeneration) [41]. So the aim of the present study is to evaluate the efficiency, safe drug delivery and less toxicity of HA-2DG over 2DG through *in silico* screening procedure. Our previous research has proven that four SARS-CoV-2 viral molecular protein targets have been analyzed with Hyaluronic Acid-Hydroxychloroquine (HA-HCQ) and the results obtained reveal better interactions with viral protein targets than the free Hydroxychloroquine (HCQ) drug. The HA-HCQ drug conjugate showed maximal drug delivery to the lower respiratory tract through CD44 receptors with increased drug clearance and less toxicity to host cells. The results of MD simulation trajectories study reveal that HA-HCQ-SARS-CoV-2 protein complexes found superior complex stability over HCQ-SARS-CoV-2 protein complexes. We confirm that HA-HCQ drug conjugate will be useful to establish a promising early stage antiviral drug for the novel treatment of COVID-19. [31].

Moreover, the molecular docking analysis of Hyaluronic Acid and Polymer-Drug Conjugate in the Target-Mediated Treatment of Cancer was reported by Gnanendra et al [42]. In this study, the activity of the cancer drug methotrexate, 3′,5′-dichloromethotrexate and ornithine-methotrexate was studied against the receptor caspase-1. Research shows that conjugation of cancer drugs to the natural polysaccharide hyaluronic acid might serve as a drug to effectively treat cancer.

The SARS-CoV-2 virus enters the cell *via* Angiotensin Converting Enzyme 2, ACE-2, receptor mediated endocytic pathway, which is composed of a series of highly dynamic membrane-enclosed tubule-vesicular structures with different biological functions such as early endosomes, late endosomes, recycling endosomes, and lysosomes. The HA-2DG Drug will enter the cell-mediated by the CD44 receptor and then under the influence of hydrolytic enzymes, released from the lysosome, splits the HA-2DG ester covalent bond releasing the 2DG drug into the cell; the 2-Deoxy-D-glucose (2-DG) acting as the D-glucose mimic interfere with the D-glucose metabolism, 2-DG inhibit glycolysis due to formation and intracellular accumulation of 2-Deoxy-D-Glucose-6-phosphate (2-DG6P), inhibiting the function of hexokinase and glucose-6-phosphate isomerase, causing nutrients and energy deprivation, and inducing death of the virus [43].

4. CONCLUSION

The present research was aimed to evaluate the safety of drug delivery, targeting receptors, toxicity, and efficacy of Hyaluronic acid-2-Deoxyglucose (HA-2DG) conjugate over free 2-Deoxyglucose (2DG) drug using molecular docking study. Four SARS-CoV-2 viral molecular protein targets such as Mpro,PLpro, RdRp and S protein have been analyzed with HA-2DG and the results obtained reveal better interactions with viral protein targets than the free 2DG drug. HA-2DG drug conjugate showed maximal drug delivery to the lower respiratory tract through CD44 receptors with increased drug clearance and less toxicity to host cells. Further studies are in progress to the synthesis of HA-2DG conjugates with different degrees of substitutions of drugs to the polymer and to evaluate the antiviral activity both in *in-vitro* and *in-vivo* towards Mpro, RdRp, PLpro and S protein targets of SAR-CoV-2. This will leads to the establishment of a promising and novel treatment option for COVID-19 and other related diseases through its versatile drug conjugation technology.

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