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Antagonizing the interplay between SARS-CoV-2 viral RNA polymerase components and the host transcriptional machinery with Thrombin, Plasmin & Cysteine Protease as a potential mechanism of interference with viral RNA synthesis

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ABSTRACT

For the expression of their genes, viruses need the host transcriptional machinery. There is a lot of evidence that suggests that cellular factors are subverted by RNA viruses, many of which are used as replication factors or translation machines for replication as well as transcription of viral RNAs. A virus uses the host cell machinery, especially human transcription factors (TFs), in order to synthesise its proteins. Therefore, we selected the TFs involved in the development of various complex diseases. The main enzymes responsible for coagulation as well as fibrinolysis, respectively, are thrombin and plasmin. It was stated earlier that due to thrombin and plasmin factor Xa along with trypsin, the infectivity of viruses with wild type SARS-spike protein was lessened to a particular extent. Our objective in this computational study was to investigate the interaction of human TFs with thrombin, plasmin and cysteine protease through molecular docking, including STAT1, TP53, NRF2, CALPAIN 10 and KCNJ11, respectively. Therefore, we define the predicted interactions between these TFs and the aforementioned molecules to infer the mechanism through which replication of viral material can be indirectly prevented through inhibiting human TFs using molecular docking analysis followed by molecular visualisation of gleaned binding data. In accordance with the docking findings for transcription factors, transcription factors that had a higher binding affinity were selected and small molecules of cysteine protease had a higher binding

affinity for E2F7, KCNJ11 thrombin and E2F7 plasmin. The actions of the transcription factors could be inhibited based on potentially small molecule interactions and could serve as a potential target. In interfering with viral gene replication and synthesis, these new perceptions into the roles of host proteins can be essential steps towards new, more powerful antivirals with fewer side effects.

Keywords: Sars-CoV-2, Covid-19, Human Transcription Factors, Thrombin, Plasmin, Cysteine Protease, molecular docking.

Abbreviations: SARS CoV 2: Severe Acute Respiratory Syndrome Coronavirus 2, RBD: Receptor Binding Domain, ORFs: Open Reading Frames, RdRP: RNA Dependent RNA Polymerase, TFs: Human Transcription Factors.

1. BACKGROUND

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) originated in Wuhan and was considered to be a global pandemic by the WHO [1]. This virus is responsible for Coronavirus disease 2019 (COVID-19). It has affected around 40 million people worldwide and is responsible for over a million deaths all over the globe [2]. The genome of SARS-CoV-2 is a single-stranded RNA. It comprises nearly 14 open reading frames (ORFs) which encode several structural as well as non-structural proteins [3]. This genome encodes 16 non-structural proteins (NSPS) and 4 structural proteins [4]. The 4 structural proteins of SARS-CoV-2 are - the S protein, the E protein, the M protein, and the N protein [5]. The S protein forms the spikes on the virus surface and helps in the attachment of the envelope of the virus to the receptors of the human host cell. It consists of the S1 and the S2 subunit. The S1 subunit comprises two subdomains, an N-terminal domain, and a C-terminal domain. Both of these subdomains function as the reception binding domain (RBD). The S2 subunit is the membrane fusing domain [6, 25, 26]. The E protein aids in the replication, assembly, and pathogenesis of the virus whereas the M protein helps in the viral assembly. The N protein along with the M protein aids in the synthesis of the nucleocapsid [7].

Viruses need the host transcriptional machinery for the expression of their genes [8]. There is a lot of evidence that indicates that RNA viruses subvert cellular factors, many of which are used for the replication & transcription of viral RNAs as replication factors or translation machinery. In the transcription and replication of viral RNA, cellular factors, therefore, play a very crucial role. The cellular factors are involved in two ways. First, they are a portion of the RNA-dependent enzyme RNA polymerase (RdRP). Secondly, they bind to the RNA template where the RNA-dependent RNA polymerase acts [9, 24].

Out of all the factors, the largest risk factor in this SARS-CoV 2 pandemic is age. People of >/= 70 years are highly likely to die if infected with the pathogen. Apart from that, a certain part of the population that has previously existing cardiovascular diseases and diabetes are in danger, standing right after the elderly people in the fatality rate chart [10,11]. The COVID-19 has affected different age groups, gender and health conditions. The mortality rate has been the highest in people above the age of 80, males have shown to be more affected by the pandemic, also, Cardiovascular Disease has the highest rate of deaths [10].

In order to synthesise its proteins, a virus uses the host cell machinery, especially the transcription factors (TFs) in humans [8]. Therefore, we selected the TFs involved in the pathogenesis of complex diseases, including Cardiovascular Disease [11] and Type 1 & Type 2 Diabetes [12,13]. A study of the interaction of these TFs with human diseases using the DisGeNet Associative Gene Disease database showed that these TFs were often associated with many kinds of diseases, including respiratory infections, skin and connective tissue diseases, musculoskeletal disorders, neoplasms, and nutritional as well as metabolic disorders. In addition, intrinsic immunity serves as the first line of protection against it if a virus enters, and it is also involved in triggering the immune response [14]. The transcription factors involved in inherent immunity have therefore been selected [8,15]. Wilk et al., showed that they can interfere with the induction of nitric oxide synthase in macrophages by blocking the activation of NF-kB TF [18]. In the treatment of tissue fibrosis, SP1 TF blocking was used by Rossert and the team to suppress extracellular matrix gene expression [19].

Plasmin and Thrombin are the primary enzymes that are involved in coagulation as well as fibrinolysis, respectively. Simmons et al. found out in 2011 that infectivity of viruses having wild type SARS-spike protein was drastically reduced because of thrombin and plasmin factor Xa along with trypsin [16]. In 2008, Shivprasad et al. concluded that cysteine proteases from the latex of the plant Asclepiadaceae mimicked the activity of thrombin and plasmin [17].

Our objective in this computational analysis was to investigate the interaction of human TFs, namely STAT1, STAT2, IRF3, IRF7, IRF9, E2F1, E2F2, E2F4, E2F5, E2F6, E2F7, E3F8, TP53, NRF2, POU4F2, ISGF3, PPARG, TCF7L2, PDX1, MAFA, CALPAIN 10, KCNJ11, ENPP1, PAX4 and NEUROG3 with thrombin, plasmin and cysteine protease by molecular docking, respectively. Therefore, to infer the technique by which replication of viral material can be indirectly prevented by inhibiting human TFs using

molecular docking analysis followed by molecular visualisation of gleaned binding data, we describe the predicted interactions between these TFs and the aforementioned molecules.

2. METHODS

By initially retrieving the PDB format from RCSB-PDB [21], the docking of several transcription factors was carried out, and later Metapocket [22] was used to identify the potential ligand-binding sites in the protein while initialising the number of pockets to three. The ligand thrombin, plasmin, and cysteine protease 2D conformer were retrieved in SDF format from PubChem [23]. In addition, a structure file generator, Cactus, was used to convert the 2D conformer to the ligand file's PDB format. AUTODOCK4 [24] predicted the molecular interactions of the smaller molecules with macromolecule targets (transcription factors). To perform docking, the protocol was used and protein-ligand interactions were visualised using Discovery Studio Visualizer.

3. RESULTS

Table 1: Molecular interactions of plasmin, thrombin, and cysteine protease with amino acids in the PDX1, calpain10, and KCNJ11

Protein	Ligand	Binding Energy	Amino acid	Bond length
PDX1	Plasmin	-4.89	GLN225	2.90
				3.02
			ASP226	3.17
			CYS227	2.59
				3.02
			THR230	2.93
			GLN225	1.89
				2.69
				3.21
				1.93
			ASP226	2.77
	Cysteine protease	-5.41	GLU224	2.99
				2.93
			GLN225	3.15
				3.11
			CYS227	2.73
				2.70
			ALA228	3.20
				2.59
				3.11

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				2.76
	Thrombin	-4.91	CYS227	3.17
			GLN225	2.19
				2.18
			ASP226	1.94
			GLN224	2.07
				2.06
			ASP226	1.88
Calpain 10	Plasmin	-1.64	GLU12	2.29
				2.04
				2.46
			GLU333	2.34
				2.16
			ARG334	1.91
	Cysteine protease	-6.25	ASP29	2.33
				2.34
			ASP391	1.79
			GLU204	1.81
	Thrombin	-5.71	HIS456	2.48
				2.34
			ALA182	2.25
				2.13
			ARG458	1.98
KCNJ11	Plasmin	-1.64	ARG301	2.99
				3.10
			ASP58	2.48
				2.02
				2.36
				2.04

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			ASP65	2.37
				2.46
				1.76
	Cysteine protease	-2.94	GLN23	2.75
			GLU229	2.35
				2.10
				2.29
			ASP204	2.04
			SER208	1.97
	Thrombin	-6.52	LYS39	2.29
			ALA178	2.17

Table 2: Molecular interactions of plasmin, thrombin, and cysteine protease with amino acids in the E2F1, E2F6, and E2F7

Protein	Ligand	Binding Energy	Amino Acid	Bond Length
E2F1	Plasmin	-3.30	PRO87	3.00
			ARG90	3.11
				3.10
				2.75
	Cysteine protease	-6.16	LYS89	2.85
			ARG90	3.12
				3.03
	Thrombin	-4.02	LYS89	2.69
			ARG90	2.73
			ARG91	3.04
				3.01
E2F6	Plasmin	-3.45	LYS175	2.97
				2.68
			ASP158	2.29

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				2.13
				2.64
			GLU154	2.16
			GLU178	2.28
				2.19
				2.02
			ASP172	1.95
	Cysteine protease	-6.00	LEU235	2.92
				2.72
			GLU237	2.32
			VAL238	2.07
				2.01
	Thrombin	-4.35	TYR185	2.00
E2F7	Plasmin	-5.68	LEU238	2.06
			GLU242	2.12
			SER326	2.19
			PRO323	2.29
	Cysteine protease	-7.88	TYR237	2.27
			GLN240	2.24
			GLU242	2.25
			ASP268	1.84
	Thrombin	No Interaction		

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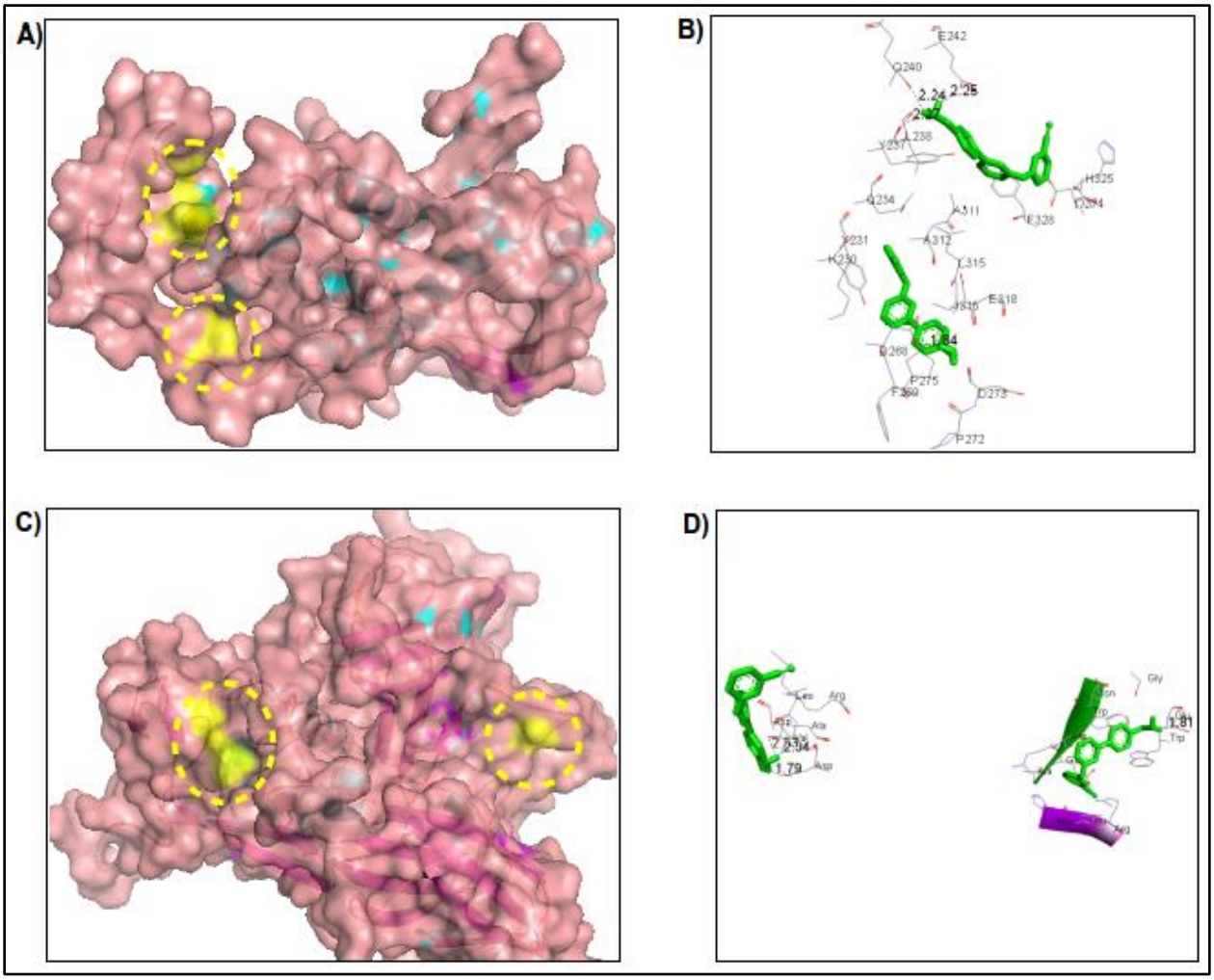

Figure 1: Intermolecular interactions of cysteine protease with amino acids in the E2F7 and Caplain10 (visualized using discovery studio visualizer and pymol). Figure 1a: Representation of molecular interaction of cysteine protease & E2F7, Figure 1b: Molecular interaction of cysteine protease & E2F7, Figure 1c: Representation of molecular interaction of cysteine protease & caplain10, Figure 1d: Molecular interaction of cysteine protease & caplain10, Key - the sticks represents cysteine protease, the secondary structure represents the E2F7 and caplain10, black dotted lines represent the interactions between the protein and ligand yellow dotted circles showcase the area of the interaction in the transcription factor.

The cysteine protease has a binding affinity of -7.88 kcal/mol with TYR237 in the E2F7 with a bond length of 2.27Å, GLN240 with a bond length of 2.24Å, GLU242 with a bond length of 2.25Å, and ASP268 with a bond length of 1.84Å. Furthermore, cysteine protease has a binding affinity of -6.25 kcal/mol with ASP29 in the calpain10 with a bond length of 2.33Å and 2.34Å. There is another interaction with ASP391 with a bond length of 1.79Å and GLU204 with a bond length of 1.81Å.

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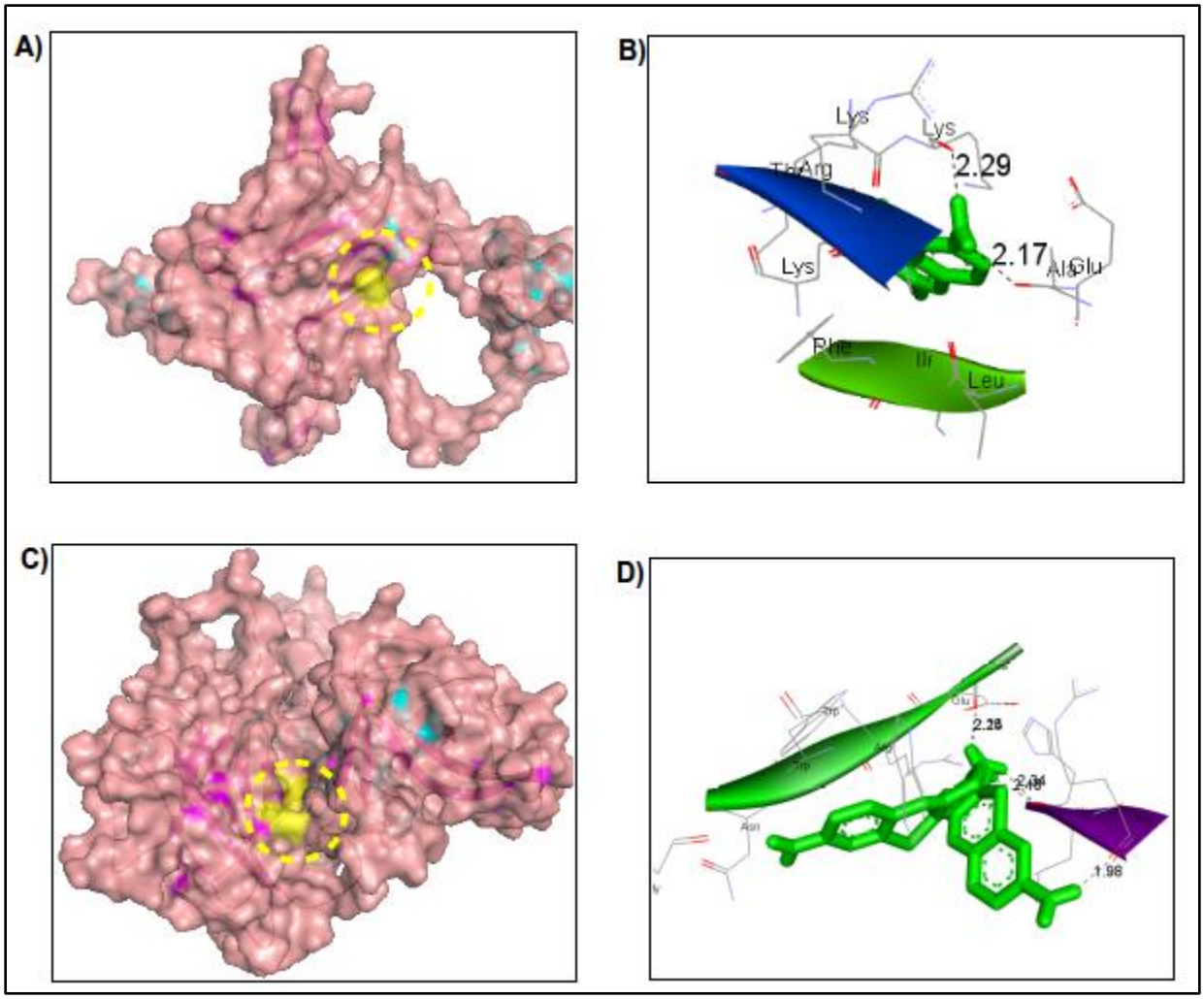

Figure 2: Intermolecular interactions of thrombin with amino acids in KCNJ11 and Caplain10 (visualized using discovery studio visualizer and pymol). Figure 2a: Representation of molecular interaction of thrombin with the KCNJ11, Figure 2b: Molecular interaction of thrombin with the KCNJ11, Figure 2c: Representation of molecular interaction of thrombin with the caplain10, Figure 2d: Molecular interaction of thrombin with the caplain10, Key - the sticks represents thrombin, the secondary structure represents the KCNJ11 and caplain10, black dotted lines represent the interactions between the protein and ligand yellow dotted circles represent the area of the interaction in the transcription factor.

The thrombin has a binding affinity of -6.52 kcal/mol with LYS39 in the KCNJ11 with a bond length of 2.29Å, and ALA178 with a bond length of 2.17Å. Furthermore, thrombin has a binding affinity of -5.71 kcal/mol with HIS456 in the calpain10 with a bond length of 2.48Å and 2.34Å. There is another interaction with ALA182 with a bond length of 2.25Å and 2.13, and ARG458 with a bond length of 1.98Å.

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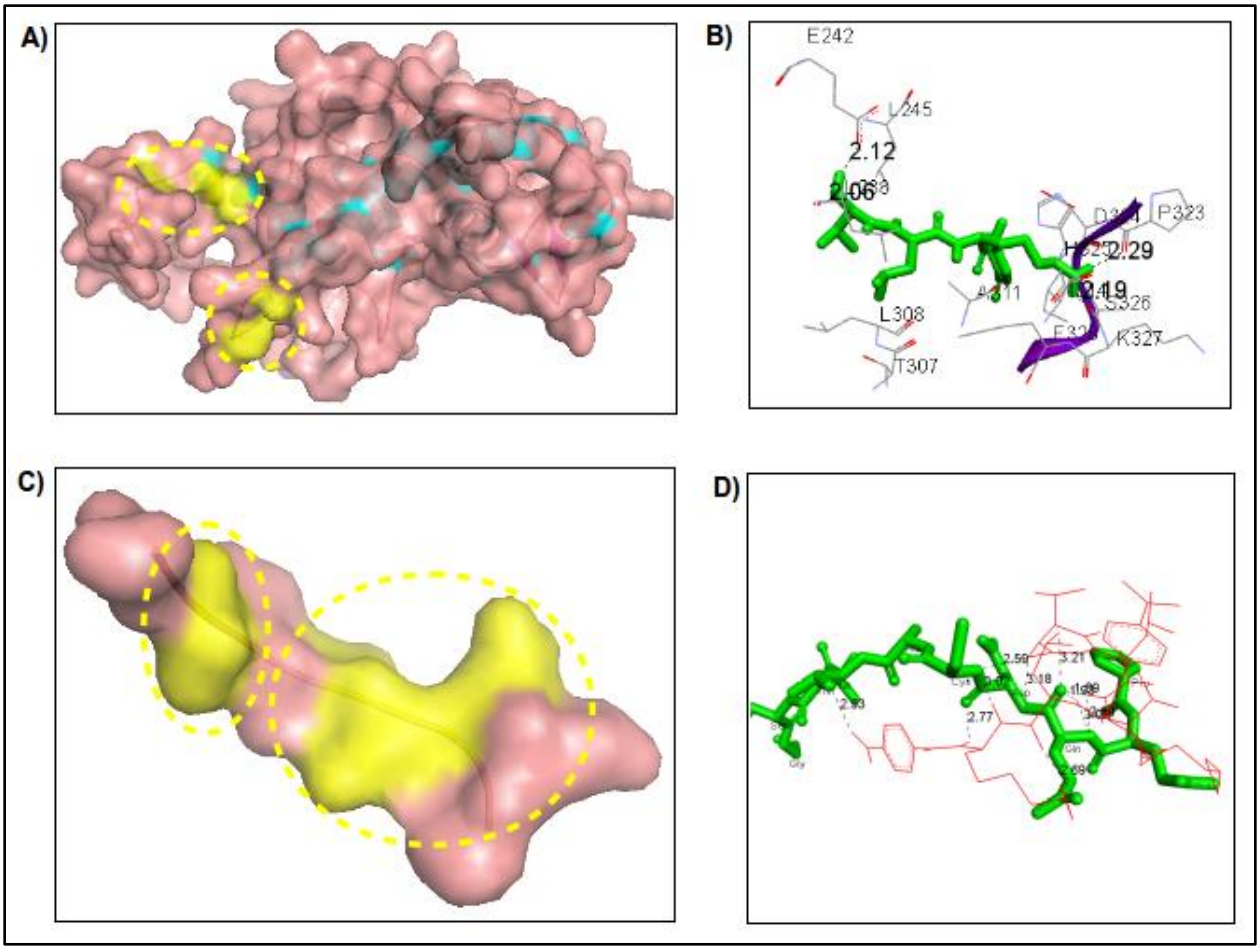

Figure 3: Intermolecular interactions of plasmin with amino acids in E2F7 and PDX1 (visualized using discovery studio visualizer and pymol). Figure 3a: Representation of molecular interaction of plasmin with the E2F7, Figure 3b: Molecular interaction of plasmin with the E2F7, Figure 3c: Representation of molecular interaction of plasmin with the PDX1, Figure 3d: Molecular interaction of plasmin with the PDX1, Key - the sticks represent thrombin, the secondary structure represents the E2F7 and PDX1, black dotted lines represent the interactions between the protein and ligand yellow dotted circles showcase the area of the interaction in the transcription factor.

The plasmin has a binding affinity of -5.68 kcal/mol withLEU238 in the E2F7 with a bond length of 2.06Å, GLU242 with a bond length of 2.12Å, SER326 with a bond length of 2.19Å, and PRO323 with a bond length of 2.29Å. Furthermore, plasmin has a binding affinity of -4.89kcal/mol with GLN225 in the PDX1 with a bond length of 2.90Å and 3.02Å. There is another interaction with ASP226 in the protein with a bond length of 3.17Å.In addition to, and interaction with CYS227 with a bond length of 2.59Å and 3.02Å, THR330 with a bond length of 2.93Å, GLN225 with a bond length of 1.89Å, 2.69Å, 3.21Å, and 1.93Å, and ASP226 with a bond length of 2.77Å.

4. DISCUSSION

The transcription factors which had a higher binding affinity were selected in correspondence with the docking results for transcription factors and small molecules (Figure 1-3, Table 2-3). Cysteine protease had a higher binding affinity with E2F7 (Figure 3A and 3B), KCNJ11 thrombin (Figure 4A and 4B) and E2F7 plasmin (Figure 5A and 5B). Based on potentially small molecule interactions, the activity of TFs could be inhibited and could serve as a potential target.

Proteolytic enzymes are crucial to several of the biological processes in species ranging from lower organisms (viruses, bacteria and parasites) to higher organisms (mammals). Proteases break down the protein molecules into smaller fragments by catalysing peptide bonds through hydrolysis. Cysteine proteases are involved in various functions namely turnover of the extracellular matrix,

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presentation of the antigens, treatment events, digestion, immune invasion, haemoglobin hydrolysis, parasite invasion, parasite discharge, and surfaced protein processing. They also promise potential drug targets for different diseases. For the prevention of undesired digestion and breakdown, cysteine proteases are synthesised as zymogens and comprised of both a regulatory as well as a mature, catalytic domain (20).

The control of transcription is the cornerstone for the processes involving the regulation of the genes. Although a cell is completely prepared for this role, viruses also rely on the host for the supply of resources for their transcription process. Through evolutionary processes, viruses have found a number of ways to optimally manipulate the host's cellular processes, such as transcription, for their personal benefit.

The pathways for viral RNA synthesis are promising targets for the development of the antiviral mechanisms, as these mechanisms are important for virus replication. However, the viral infection programs can help recognise additional weak spots via developing an understanding as to how the viruses control their gene expression and unravelling the complex ways in which these pathways are intertwined with the host transcription. Many antivirals have adverse side effects due to the inadequate understanding of the target molecule and mechanism of the virus. Here we have attempted to explain new insights into the functions of host proteins in interference with viral gene replication and synthesis, and these may be important steps towards new, more efficient antivirals with fewer side effects.

5. CONCLUSION

To conclude, viral RNA-dependent RNA synthesis can be as complex as DNA-dependent RNA transcription, involving several RNA – protein and protein-protein interactions between viral RNA or protein and cellular RNA factors. Thus, host cells are not just bystanders, but active participants in the viral RNA transcription and replication process are involved. Identification of the proteins that interfere with the virus-host interplay will speed up our efforts to unlock many of the mysteries of replication and transcription of viral RNAs.

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Ethical approval
Not applicable.

Conflict of Interest:
The authors declare that there are no conflicts of interests.

Data and materials availability:
All data associated with this study are present in the paper.

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