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ORIGINAL ARTICLE

Computational approach to decipher cellular interactors and drug targets during co-infection of SARS-CoV-2, Dengue, and Chikungunya virus

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Abstract The world is reeling under severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, and it will be frightening if compounded by other co-existing infections. The co-occurrence of the Dengue virus (DENV) and Chikungunya virus (CHIKV) has been into existence, but recently the co-infection of DENV and SARS-CoV-2 has been reported. Thus, the possibility of DENV, CHIKV, and SARS-CoV-2 co-infection could be predicted in the future with enhanced vulnerability. It is essential to elucidate the host interactors and the connected pathways to understand the biological insights. The in silico approach using Cytoscape was exploited to elucidate the common human proteins interacting with DENV, CHIKV, and SARS-CoV-2 during their probable co-infection. In total, 17 interacting host proteins were identified showing association with envelope, structural, non-structural, and accessory proteins. Investigating the functional and biological behaviour using PANTHER, UniProtKB, and KEGG databases uncovered their association with several cellular pathways including, signaling pathways, RNA processing and transport, cell cycle, ubiquitination, and protein trafficking. Withal, exploring the DrugBank and Therapeutic Target Database, total seven druggable host proteins were predicted. Among all integrin beta-1, histone deacetylase-2 (HDAC2) and microtubule affinity-regulating kinase-3 were targeted by FDA approved molecules/ drugs. Furthermore, HDAC2 was predicted to be the most significant target, and some approved drugs are available against it. The predicted druggable targets and approved drugs could be investigated to obliterate the identified interactions that could assist in inhibiting viral infection.

Keywords Cellular interactors · Covid-19 · Viral inhibitor · Viral-host protein interactions

Introduction

The pandemic caused by Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has put immense pressure on the health care system and resulted in the indefinite future. Its genome consists of positive single-stranded RNA (genus *betacoronavirus*) comprising 14 open reading frames (Orfs) which encodes 16 non-structural proteins (nsP1-16), four structural (S, E, M and N) and nine accessory proteins (orf3a, orf3b, orf6, orf7a, orf7b, orf8, orf9b, orf9c and orf10). SARS-CoV-2 may confound seasons, and its transmission is not dependent on specific temperature conditions [21]. Dengue virus (DENV) and Chikungunya virus (CHIKV) infections become prevalent during monsoon season in tropical and subtropical countries. Mosquito species *Aedes aegypti* is the major vector for the transmission of DENV as well as CHIKV [45, 55]. There are reports that the severity of the disease is much more than the mono-infection during their co-infection [29, 45, 55]. SARS-CoV-2 and DENV infections have also been reported to share clinical and laboratory features [72]. Accumulated data from Singapore [72], India [3, 25], and Mayotte (Island in the Indian Ocean) [15] suggested that the patients have a probability of being co-

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infected with SARS-CoV-2 and DENV. A report from Thailand reported that the SARS-CoV-2 patients exhibited symptoms like skin rash with petechiae and low platelet count initially, which are common clinical manifestations during DENV infection [27]. Though the co-infection of CHIKV and SARS-CoV-2 is not reported yet, the probability in the future exists. Furthermore, the co-incidence of DENV, CHIKV, and SARS-CoV-2 at the same time could also be predicted with more severity in DENV/CHIKV predominant areas. SARS-CoV-2 is one of the greatest challenges of recent times, and its interaction with host proteins during co-infection needs to be deciphered.

Both DENV and CHIKV are single-stranded RNA viruses that belong to genus *flavivirus* and *alphavirus*, respectively [29]. The genome of CHIKV encodes four nsPs (nsP1-4) and five structural proteins (E1, E2, E3, 6 K and C) while DENV encodes seven nsPs (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5) and three structural proteins (C, prM, and E) [38, 56].

SARS-CoV-2, DENV and CHIKV infections have been strongly associated with marked increase in inflammatory cytokines. Higher concentrations of pro-inflammatory cytokines have been reported in the severely critically ill patients of coronavirus disease (Covid-19) [7, 74]. The cytokine storm was reported to be responsible for the tissue damage (heart, liver, and kidney) and multiple organ failure [14]. Studies have demonstrated the association of cardiovascular manifestations during CHIKV and DENV infections due to enhanced up-regulation of cytokines [1, 57]. Thus, the cytokine storm and the multi-organ dysfunction have been observed during the mono-infections of CHIKV, DENV and SARS-CoV-2.

The characterization of interactions between viral and host proteins help to understand the molecular mechanism of infection. Several studies have reported the interactions of human proteins with DENV and CHIKV during mono-infection [14, 33, 43]. However, the data about SARS-CoV-2 infection is limited [23, 55]. The study of viral-host protein interactome during co-infection will help to understand the residing mechanism adopted by the virus for its replication and pathogenesis.

In the present study, the viral-host protein–protein interactions were analysed during the co-infection of DENV, CHIKV, and SARS-CoV-2 using in silico approach. The cellular interactors during mono-infections were obtained from the published studies. The interactome network of each disease was constructed and merged to identify the cellular interactors during co-infection. The biological and molecular functions of identified proteins, as well as the associated pathways, were analysed. Moreover, the drug target proteins were predicted, which could be targeted to liquidate DENV, CHIKV, and SARS-CoV-2 co-infection.

Materials and methods

Collection of data

The data of human host interactors of DENV, CHIKV, and SARS-CoV-2 mono-infections were collected from the published studies [14, 21, 43]. Doolittle et al. and Rana et al. identified the host interactors using computationally approaches for DENV and CHIKV, respectively. They used structural similarity approach with the human proteins, followed by utilization of databases, Biological General Repository for Interaction Datasets (BIOGRID), and Human Protein Reference Database (HPRD), for identifying human interactors [14, 43]. Gordon et al. utilized the affinity purification mass spectrometry (AP-MS) approach to identify the cellular interactors of SARS-CoV-2 [21].

Identification of cellular interactors during co-infection

The network of accumulated host protein interactions data during mono-infections was constructed using the STRING online tool [60] and then imported in Cytoscape [52]. The in-built merge tool in Cytoscape was utilized to merge the individual three networks. The merging of data yielded a group of human proteins that were common in all three individual proteins networks.

Functional analysis

The biological and functional analyses of identified proteins were studied to understand the cellular response during co-infection. The Protein Analysis Through Evolutionary Relationships (PANTHER) tool, Kyoto Encyclopedia of Genes and Genomes (KEGG) database, and the Universal Protein Resource (UniProt) Knowledgebase (UniProtKB) were exploited to study the functions and the linked pathways [28, 62, 63]. The PANTHER tool facilitated the molecular and biological functions as well as processes of uncharacterized genes/proteins based on the evolutionary relationships [62]. UniProtKB is a comprehensive resource for protein sequence and annotation data [75] and KEGG database assisted in deciphering the functional behaviours of gene, biological pathways, and diseases [28].

Identification of drug targets protein

The identified human proteins were further analysed to be defined as drug targets. DrugBank [69], and Therapeutic Target Database (TTD) [67] were used in the study for the

prediction of the druggable proteins. The DrugBank database is a unique bioinformatics and cheminformatics resource that combines detailed drug data with comprehensive drug target information. The DrugBank (version 5.1.6) comprises of 13,570 drug entries including 2631 approved small molecule drugs, 1377 approved biologics (proteins, peptides, vaccines, and allergenics), 131 nutraceuticals and over 6373 experimental (discovery-phase) drugs. Additionally, 5252 non-redundant protein (i.e. drug target/enzyme/transporter/carrier) sequences are linked to these drug entries. Each entry contains more than 200 data fields with half of the information being devoted to drug/chemical data, and the other half devoted to drug target or protein data [69]. Furthermore, TTD contains the known and explored therapeutic protein and nucleic acid targets, the targeted disease, pathway information, and the corresponding drugs directed at each of these targets [67].

Results and discussion

Decode host interactors during co-infection

The data of human protein interactions with DENV, CHIKV, and SARS-CoV-2 during mono-infections were collected for further analysis [14, 21, 43]. The networks of human proteins during viral mono-infections were constructed using Cytoscape and observed to be densely interconnected. The construction of proteome network and its analysis using Cytoscape have also been utilized to study protein–protein interactions for other viruses including the Hepatitis C virus (HCV) [17], Hepatitis B virus (HBV) [54], and gynaecological cancer [31]. The human interactors during the co-infection of DENV, CHIKV, and SARS-CoV-2 were elucidated by the merged constructed networks. It was observed that the total 17 human interactors shared in all the three networks could act as cellular interacting partners for viral proteins during co-infection (Table 1). The same strategy was also exploited to identify the common nodes and the novel candidate biomarkers during HBV and HCV co-infection [54]. Taz et al. generated the protein–protein interaction network during dengue, malaria, and chikungunya disease to elucidate the common genes present in all the three diseased conditions as drug targets. This computational approach is a powerful tool to study the hub of genes, proteins, and pathways related to the diseased conditions [61].

Moreover, it was observed that most elucidated host proteins mainly interacted with the nsPs and few structural (mainly envelope) proteins. It could be predicted that the interactions involved with nsPs might influence the RNA synthesis, replication, and viral life cycle. Host proteins interacting with the envelop proteins might affect the viral entry, virion formation, as well as virulence.

Functional analysis of identified proteins

The cellular functions and the associated pathways of the identified interactors of DENV, CHIKV, and SARS-CoV-2 during co-infection were analysed using the KEGG database, Panther tool, and UniProtKB (Table 2). It was found that the identified proteins were involved in signaling pathways, RNA transport and processing, ubiquitination, vesicle trafficking, innate and adaptive immune responses. These pathways help to understand viral biology in relation to cellular and molecular mechanisms.

One of the identified proteins in the study was integrin beta 1 (ITGB1), as a cell adhesion receptor is exploited by viruses to make a successful entry into the host cell. The up-regulation of ITGB1 has been reported in CHIKV, DENV and SARS coronavirus (SARS-CoV) infections [10, 11, 58]. ITGBI was also reported to be crucial to maintain the infection of flaviviruses like HCV [75] and the West Nile virus (WNV) [50]. Therefore, it could be predicted that during DENV, CHIKV, and SARS-CoV-2 co-infection, their interaction with the host's ITGB1 might assist the viral entry and disseminate infection.

The identified interactors, Ras homolog family member A (RHOA) and ITGB1, have been associated with the phosphatidylinositol-3-kinase (PI3K)/Akt and the mammalian target of rapamycin (mTOR) signaling pathways. CHIKV has been reported to utilize this pathway for its replication [13]. Liu et al. reported the modulation of the PI3K-Akt pathway to induce apoptosis during DENV infection [30].

The common interactor identified in the study, Poly(A)-binding protein cytoplasmic 1 (PABPC1), is a member of poly(A) binding proteins (PABP) family, which plays multiple roles in regulating the mRNA stability, mRNA metabolism and RNA transport. Suzuki et al. reported that the binding of PABPC1 with the A-rich region in the 3′UTR of DENV mRNA positively regulated its translation [59]. Its interaction with the nsP2 protein of CHIKV [6] and N protein of SARS-CoV-2 was also reported [21].

Another identified interactor, Ring box protein-1 (RBX1), is a component of ubiquitin–proteasome pathways (UPP) that has been shown to regulate the protein stability and protein trafficking [19]. RBX-1 is also associated with the Wnt signaling pathway, which is critical to control cell cycle, development, cell motility, and cell death. RBX-1 was reported to be differentially expressed during CHIKV infection. Though, the upregulation of its associated pathways was observed during DENV, WNV, Japanese encephalitis virus (JEV), and Human immunodeficiency virus (HIV) infections [19, 70, 76].

Table 1 The identified human proteins as interactors of DENV, CHIKV, and SARS-CoV-2 during co-infection

S. nos	Identified host proteins	CHIKV	DENV	SARS-CoV-2
1	ITGB1	nsP4, E1, E2	NS1, NS4B, E	orf8
2	RHOA	E1, E2	NS4A, NS4B, E, C	nsP7
3	NUP214	nsP2, nsP3, nsP4, E3, 6 K	NS2A, NS4B, NS3, NS1	nsP9
4	NUP62	nsP2, nsP3, E3, 6 K	NS2A, NS4B, C, NS3	nsP9
5	PABPC1	nsP2, nsP4,6 K,	NS2A, NS4B, C	N
6	RBX1	6 K	NS2A, NS4B, C	orf10
7	HDAC2	nsP2, nsP3, E3	E, NS3, NS1	nsP5
8	TLE1	nsP2, E1, E2	C, E, NS3, NS1	nsP13
9	MARK3	nsP4, 6 K	NS2A, NS4B,	orf9b
10	ARF6	nsP2, E3	NS4A	nsP15
11	UPF1	6 K, E1, E2, nsP1, nsP2	NS4B, NS3	N
12	RALA	E1	E	nsP7
13	CEP250	nsP4	NS2A, NS4B,	nsP13
14	F2RL1	C	NS3	orf9c
15	SRP19	E3, 6 K, nsP4	NS2A, NS4B	nsP8
16	NUP98	E3, 6 K, nsP4	NS4B, C, NS1, NS2A	orf6
17	SLC9A3R1	E1, E3, nsP1, nsP3	NS2A, NS4B	orf9b

The nuclear pore complexes (NPC) present in the nuclear envelope are composed of nucleoporins (NUPs) and act as multiprotein channels. The NPC acts as a selective barrier for bidirectional transport of RNA, viral proteins, and molecules from the nucleus to the cytoplasm. The viruses could hijack this trafficking by remodelling the nuclear membrane, redirecting the host machinery for its own replication and combat anti-viral response [46]. In the current study, Nup214, NUP62, and NUP98 were identified as shared host interactors for the SARS-CoV-2, DENV, and CHIKV viruses. It is known that CHIKV, DENV, and SARS-CoV-2 primarily replicate in host cytoplasm, but intriguingly, some of the viral proteins get localised into the nucleus, which is essential for maintaining their infection [41, 44, 71]. NUP98 was reported to be accumulated in the nucleus with the nsP3 protein of CHIKV, but the relation is still unexplored [44]. The cleavage and degradation of NUP98 and NUP62 by the serine protease activity of NS2B-NS3 were observed during DENV infection. This degradation significantly inhibited the mRNA export through the NPC [8]. Nucleoporins (NUP98, NUP214, and NUP62) have been reported as interactors of SARS-CoV-2 and interfered in nuclear export, but the detailed mechanism is unknown [21]. Moreover, NUP98 and NUP214 were reported to be crucial in many other viral infections [24, 39, 48, 51].

Up-frame shift 1 (UPF1) is an ATP-dependent RNA and DNA helicase involved in nonsense-mediated mRNA decay (NMD), part of the eukaryotic RNA surveillance pathway [18]. UPF1 interacts with the initiation factors during translation and releases the ribosome to degrade mRNAs containing premature stop codons. Balistreri et al. observed that depletion of UPF1 with other co-factors resulted in the increased infection of the Semliki Forest virus (SFV, *alphavirus*) and hence, concluded that the UPF1 was involved in the early steps of infection to reduce the synthesis of viral RNA and proteins [4]. Moreover, the N protein of SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV) has been shown to suppress the NMD pathway to protect its mRNA from degradation and ensure efficient replication [65].

Another identified interactor, a histone deacetylase-2 (HDAC2), plays a crucial role in transcriptional regulation, cell cycle progression, and developmental events [12]. HDAC2, primarily located in the nucleus, is reported to have an essential role in regulating the inflammatory response of macrophages. HDAC2 is associated with the TNF signaling as well as longevity regulating pathway. It was reported that dengue hemorrhage with a high TNF level caused the endothelial cells apoptosis resulting in vascular damage [73]. Although the molecular insight of HDAC2 is not fully understood, it was reported to be crucial for viral infections like Influenza A virus (IAV) [37] and Human alphaherpesvirus 1 (HSV-1) [66].

Identified interactor, microtubule affinity-regulating kinase 3 (MAPK3) accounts for the specific phosphorylation of microtubule-associated proteins and linked with the intracellular signal transduction pathways. F2RL1 (coagulation factor II (thrombin) receptor-like 1), was found as a common interacting host protein during CHIKV, DENV,

Table 2 The functions and pathways linked with the identified host proteins

S. nos	Identified host proteins	Function	Associated pathways
1	ITGB1	Cell adhesion, cellular defense response	Phagosome, PI3K-Akt signaling pathway, Rap1 signaling pathway
2	RHOA	Cytoskeleton organization, regulate cellular responses such cytoskeletal dynamics, cell migration and cell cycle	Ras signaling pathway, Rap1 signaling pathway, cAMP signaling pathway, Chemokine signaling pathway, mTOR signaling pathway, Wnt signaling pathway, Endocytosis, Sphingolipid signaling pathway, Phospholipase D signaling pathway
3	NUP214	Nucleocytoplasmic transport	RNA transport
4	NUP62	Nucleocytoplasmic transport, involved in mitotic cell cycle progression	RNA transport
5	PABPC1	Regulates processes of mRNA metabolism	RNA transport, mRNA surveillance pathway, RNA degradation
6	RBX1	Ubiquitination and proteasomal degradation	Cell cycle, HIF-1 signaling pathway, Nucleotide excision repair, Protein processing in endoplasmic reticulum, Wnt signaling pathway, TGF-beta signaling pathway
7	HDAC2	Deacetylase activity, transcriptional regulation, cell cycle progression	Cell cycle, Notch signaling pathway, TNF signaling Longevity regulating pathway, Thyroid hormone signaling pathway
8	TLE1	Transcriptional corepressor	Transcription corepressor activity
9	MARK3	Serine/threonine-protein kinase and Phosphorylation of microtubule-associated proteins	Intracellular signal transduction, MAPK cascade
10	ARF6	Protein trafficking that regulates endocytic recycling and cytoskeleton remodeling	Ras signaling pathway, Phospholipase D signaling pathway, Endocytosis, Fc gamma R-mediated phagocytosis
11	UPF1	Nonsense-mediated mRNA decay	RNA transport, mRNA surveillance pathway
12	RALA	Involved in cellular processes including gene expression, cell migration, cell proliferation, oncogenic transformation, and membrane trafficking	Ras signaling pathway, Rap1 signaling pathway, Phospholipase D signaling pathway
13	CEP250	Ciliogenesis	Involved in centrosome cohesion during interphase
14	F2RL1	Involved in the activation of several signaling pathways including phospholipase C, intracellular calcium, mitogen-activated protein kinase (MAPK), I-kappaB kinase/NF-kappaB and Rho	Inflammatory mediator regulation of TRP channels, Neuroactive ligand-receptor interaction
15	SRP19	Cotranslational protein targeting to membrane	Protein export
16	NUP98	Nucleocytoplasmic transport	RNA transport
17	SLC9A3R1	Actin cytoskeleton organization	Tight junction, parathyroid hormone synthesis, secretion, and action

and SARS-CoV-2 co-infection in the current study. F2RL1 is also known as protease-activated receptor 2 (PAR2) and belongs to the family of G protein-coupled receptors. It accounts for the inflammatory process and modulates the immune response mediated by toll-like receptors (TLR) signaling and macrophages during viral infection [2]. Schanoski et al. reported the production of Granzyme A, which was correlated to PAR-1 and PAR-2, responsible for the inflammation and swelling induced during CHIKV, but the exact mechanism is not known [49]. Moreover, the activation of PAR2 was reported to modulate HIV and IAV infections [2].

Another identified protein, ADP Ribosylation Factor 6 (ARF6), is a membrane trafficking protein that coordinates the plasma membrane dynamics and regulates the internalization of cargo via endocytosis [64]. GTPase-activating proteins (GAP) are generally required for the regulation (activation and inactivation) of Arf6. In the case of DENV, the type I interferons (IFN-I) up-regulated the expression of ADAP2 (ArfGAP domain-containing protein 2), a GTPase-activating protein for Arf6, that suppressed its infection primarily at the stage of viral entry [53, 64]. Moreover, Radoshitzky et al. reported ARF6 in association with other host factors were involved in alphaviruses trafficking [42].

Table 3 The summary of predicted drug target proteins

S. nos.	Druggable proteins	Proposed molecules	Molecule type	Indication	Source
1	ITGB1	Anti-thymocyte globulin (rabbit)	FDA approved drug	ITGB1 prevents renal transplant rejection, binds to multiple, T-cell specific antigens leading to T-lymphocyte cell death via complement mediated cytotoxicity or apoptosis	DrugBank
		131I-radretumab	Antibody	Completed Phase 1/2 clinical trials to treat Non-small-cell lung cancer	TTD
2	HDAC2	Vorinostat	Small molecule and FDA approved	Vorinostat is indicated for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma	DrugBank
		Pracinostat	Small molecule and investigational	Pracinostat is indicated for the treatment of various forms of cancer	
		Lovastatin	Small molecule and approved	Lovastatin is indicated to treat hypercholesterolemia. It reduces the risk of Coronary Heart Disease (CHD), Dyslipidemia, Heterozygous Familial Hypercholesterolemia, High Cholesterol, Peripheral Artery Disease, Primary prevention Coronary artery disease, Primary prevention Myocardial infarction, Primary prevention Unstable angina	
		Valproic acid	Small molecule and approved	Valproic acid is indicated for the treatment of seizures	DrugBank
		Romidepsin	Small molecule and approved	It is indicated to treat cutaneous T-cell lymphoma	DrugBank
		Simvastatin	Small molecule and approved	Simvastatin is indicated to treat hyperlipidemia and it reduces the risk of cardiovascular events	DrugBank
		Pravastatin	Small molecule and approved	Pravastatin is indicated for the prevention of coronary events	DrugBank
		Fluvastatin	Small molecule and approved	It is indicated as an adjunct to dietary therapy to prevent cardiovascular events (Atherosclerosis, Cardiovascular Heart Disease)	DrugBank
		Atorvastatin	Small molecule and approved	Atorvastatin is indicated to treat several types of dyslipidemias	DrugBank
		CHR-3996	Small molecular drug	Phase 1 clinical trials to treat solid tumour/cancer	TTD
3	MARK3	Fostamatinib	Small molecule and approved	Indicated for the treatment of chronic immune thrombocytopenia	DrugBank
		CBP-501	Small molecular drug	Phase 1 clinical trials to treat solid tumour/cancer	TTD
4	ARF6	Myristic acid	All are small molecules and experimental	Myristic acid is indicated to be highly effective against tumor	DrugBank
		5′-Guanosine-diphosphate-monothiophosphate	Small molecule and experimental	Not available	DrugBank
		Guanosine-5′-Diphosphate	Small molecules and experimental	Not available	DrugBank
5	RALA	Guanosine-5′-Diphosphate	Small molecules and experimental	Not available	DrugBank
6	RhoA	Guanosine-5′-Diphosphate	Small molecule and experimental	Not available	DrugBank
7	F2RL1	Amidine compound 6	Small molecular drug	Indicated for inflammation	TTD

Furthermore, it was required for entry and early infection during HIV infection [20].

Identification of druggable proteins

The identified human interactors were further studied to predict drug target proteins using databases like DrugBank and TTD. The databases contain the necessary information regarding the drug targets, approved drugs, and experimental drugs that were exploited in the current study to elucidate the possible drug targets [67, 69]. Among the identified cellular interactors, seven human proteins were identified and predicted as druggable targets. The information regarding the identified target proteins, agonist, purposed molecules/ drugs, along with their indications, are summarised in Table 3. It was analysed that ITGB1, HDAC2, and MARK3 human proteins were targeted by FDA approved small molecules/ drugs. At the same time, the other predicted druggable proteins were targeted by the small molecules, which are present either in the experimental phase or in the clinical phase.

Moreover, the human protein HDAC2 was observed to be targeted by nine FDA approved drugs emphasizing it to be a significant druggable protein. Additionally, the approved molecules/drugs targeting HDAC2 were observed to be effective for the inhibition of other viral infections. Vorinostat, an HDAC inhibitor used in the treatment of lymphoma, was reported to significantly abrogate the genome replication of Human papillomaviruses via induction of apoptosis, shown as a promising therapeutic agent [5]. Antiviral activity of lovastatin has been reported against Respiratory syncytial virus (RSV) [22], DENV Serotype 2 [34], Zika virus [16], and HIV-1 [32].

Montoya et al. suggested that the administration of lovastatin as anti-HIV-1 in chronically infected patients was safe [36]. Martinez-Gutierrez et al. suggested that lovastatin delayed the progression of DENV-2 in infected mice [34]. However, Whitehorn et al. did not observe any clinical benefits while treating DENV infected adults with lovastatin [68]. Gower et al. reported that lovastatin inhibited RSV by reducing the production of cholesterol and isoprenylation of RhoA [22]. Moreover, atorvastatin, simvastatin, and pravastatin were considered conventional therapeutics for IAV-H1N1, as these approved molecules effectively reduced the cytokines profile in the H1N1 infected cells [35]. Additionally, the use of statins (class of drugs) for the treatment of COVID-19 has been predicted as they help to reduce the level of cholesterol, anti-inflammatory, and immunomodulatory activities [40]. Another approved molecule, valproic acid targeting HDAC2, has been reported to significantly inhibit the HSV infection in an oligodendrocyte cell line [9].

Recently, in silico study revealed that the fostamatinib (FDA approved drug) has the potential to treat COVID-19. Fostamatinib, approved for chronic immune thrombocytopenia, is an inhibitor of spleen tyrosine kinase (Syk), an important signalling component in immune cells. The docking of fostamatinib with the protease of SARS-CoV-2 had the highest docking score compared to other drugs like hydroxychloroquine, remdesivir, favipiravir, and darunavir, which have the potential to treat COVID-19 [47]. Additionally, fostamatinib is in phase 2 clinical trial to treat COVID-19 patients [26] as it can control dysregulated immune system responsible for the underlying symptoms of SARS-CoV-2. In the present study, MARK3 was found to be the possible host target of fostamatinib to be explored further.

The chances of co-infection of arboviruses (DENV and CHIKV) with SARS-CoV-2 predicted during the rainy season because of the favourable breeding conditions for the mosquitoes, and the current pandemic of SARS-CoV-2 could severely affect the human health. Deciphering the viral-host interactions assist in understanding the viral biology as well as the cellular mechanism. The present study elucidates the interacting cellular proteins and druggable targets that could play a crucial role during the co-infection of DENV, CHIKV, and SARS-CoV-2. The identified proteins were linked with several cellular and signaling pathways that might be crucial for sustained viral infection. Moreover, the approved therapeutic molecules against the potential drug target proteins were predicted in the study. Eventually, these interactions could be confirmed and utilized to develop effective therapeutics.

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Declaration

Conflict of interest The authors declare that there is no conflict of interest.

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