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Identification and host response interaction study of SARS-CoV-2 encoded miRNA-like sequences: an *in silico* approach

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ABSTRACT

COVID-19, a global pandemic caused by an RNA virus named SARS-CoV-2 has brought the world to a standstill in terms of infectivity, casualty, and commercial plummet. RNA viruses can encode microRNAs (miRNAs) capable of modulating host gene expression, and with that notion, we aimed to predict viral miRNA like sequences of MERS-CoV, SARS-CoV and SARS-CoV-2, analyze sequence reciprocity and investigate SARS-CoV-2 encoded potential miRNA-human genes interaction using bioinformatics tools. In this study, we retrieved 206 SARS-CoV-2 genomes, executed phylogenetic analysis, and the selected reference genome (MT434792.1) exhibited about 99% similarities among the retrieved genomes. We predicted 402, 137, and 85 putative miRNAs of MERS-CoV (NC_019843.3), SARS-CoV (NC_004718.3), and SARS-CoV-2 (MT434792.1) genome, respectively. Sequence similarity was analyzed among 624 miRNAs which revealed that the predicted miRNAs of SARS-CoV-2 share a cluster with the clad of miRNAs from MERS-CoV and SARS-CoV. Only SARS-CoV-2 derived 85 miRNAs were encountered for target prediction and 29 viral miRNAs seemed to target 119 human genes. Moreover, Kyoto Encyclopedia of Genes and Genomes (KEGG) and Gene Ontology (GO) analysis suggested the involvement of respective genes in various pathways and biological processes. Finally, we focused on eight putative miRNAs influencing 14 genes that are involved in the adaptive hypoxic response, neuroinvasion and hormonal regulation, and tumorigenic progression in patients with COVID-19. SARS-CoV-2 encoded miRNAs may cause misexpression of some critical regulators and facilitate viral neuroinvasion, altered hormonal axis, and tumorigenic events in the human host. However, these propositions need validation from future studies.

1. Introduction

The Corona Virus Disease-2019 (COVID-19) has emerged as a public health emergency with a vast number of cases and death tolls. It has reached the magnitude of a 'Global Pandemic' with 216 countries held captive by its atrocious clinicopathological consequences, loss of productivity and gross economic downfall [1–3]. This highly contagious zoonotic disease is caused by a single-strand, enveloped RNA virus native to the 'Coronaviridae' family that genetically resembles severe acute respiratory syndrome coronavirus (SARS-CoV) of 2002–2003, and

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hence nominated as SARS-CoV-2 [4–9]. COVID-19 is transmissible via direct contact, fomites or aerosol droplets generated from spitting, sneezing or coughing by an infected person [10]. After entry into the host, the median time for incubation is an estimated 4–5 days extending up to 14 days [11–13]. Clinically, SARS-CoV-2 manifests a number of symptoms such as fever, fatigue, malaise, headache coupled with pneumonia or acute respiratory distress syndrome (ARDS) [14]. Although the initial infection harbors in the lungs, it may develop viremia with a risk of multisystem involvement leading to septicemia and organ failure [15–17]. Extra-pulmonary conditions include neurologic involvement (stroke, loss of smell or taste), cardiovascular symptoms (myocardial dysfunction, arrhythmia, acute coronary syndromes), renal damage (acute kidney injury), gastrointestinal distress (nausea, vomiting, diarrhea, loss of appetite), hepatocellular injury and metabolic derangements (hyperglycemia and ketosis) [18–21]. Immuno-compromised individuals with coexisting illnesses for instance, cardiovascular disease, hypertension, diabetes, asthma, malignancy and chronic diseases are the highest vulnerable cohort for COVID-19 [22,23]. Studies have reported higher mortality rates in aged and male patients (>60 years; Male:Female = 1.7:1) with additional comorbidities such as cardiovascular disease (13.2%), diabetes (9.2%) and hypertension (8.4%) [19,24].

In recent years, microRNAs (miRNAs) have gained much attention as a post-transcriptional regulatory molecule leading to pathogenicity of disease [25]. These are minuscule non-protein-coding endogenous RNA molecules, capable of regulating approximately 50% of all mammalian protein-coding genes involved in various pathophysiologic mechanisms in eukaryotic organisms [26–28]. More than 200 viral miRNAs have hitherto been identified that regulate cellular and viral gene expression [29]. Contrary to the impossibility of RNA virus to encode miRNAs due to inaccessibility of the pathogen to cellular miRNA processing machinery [29–32], recent studies have confirmed that RNA viruses including the engineered influenza virus [33], Hepatitis A virus (HAV) [34], Hepatitis C virus [35], H5N1 Influenza [36], Ebola virus [32] and HIV-1 [37] can produce miRNAs. Usually, 5′ nucleotides of 2–7 of the mature miRNAs bind to the complementary sequences in 3′ UTRs of target messenger RNAs and may lead to a large pool of targets [38]. Different miRNAs can also target multiple sites on a single transcript [39,40]. However, if the viral miRNAs target in imperfect complementarity, that results in translational repression and mRNA destabilization [41,42]. Hence, RNA viruses can use the miRNA biogenesis pathway to produce modulatory molecules for mRNA manipulation [43]. Viral miRNAs can regulate the interaction with different biological processes comprising metabolism, growth, apoptosis, differentiation, proliferation and angiogenesis [44–46], and take part in replication, inhibition, pathogenesis and disease progression via genomic binding or interfering in host transcriptome activities [47–49]. Previous research has hinted towards miRNAs to have a role in the development of stroke, cardiovascular disease, inborn error of metabolism, endocrine disorder, metabolic disease, autoimmune disease, neurodegenerative ailment, retinal disorder and carcinoma [50–54].

Prior literature has delved into the role of viral miRNAs in fetal developmental anomalies due to the Zika virus [55], dampening of cell-mediated immunity by the Ebola virus [32], enhanced cytokine signaling by influenza virus [36]. Post-COVID-19 computational studies have focused on prediction of mature viral miRNA, their functions, exchanges between viral miRNA-cellular gene, and the impact of aging and health conditions on such interactions [56–59]. Following the trend, we performed an *in silico* analysis to predict the putative miRNAs of SARS-CoV-2 and their targeted host genes. Moreover, we aimed to explore possible host-virus interactions to gain further insight into the viral pathogenicity and correlate the findings with current clinical data.

2. Methodology

2.1. Retrieval of genome sequences and construction of phylogenetic analysis

The genomes of MERS-CoV (NC_019843.3), SARS-CoV (NC_004718.3) and SARS-CoV-2 were collected from GISAID (https://www.gisaid.org/) and from NCBI (https://www.ncbi.nlm.nih.gov/) database. Before the phylogeny reconstruction, multiple sequence alignment of the sequences was performed using mafft –auto option (version 7.455; [60]. RAxML−V8.2.12 [61]; was used for the phylogenetic tree construction using GTRGAMMA as the best substitution model, identified by PartitionFinder−V2.1.1 [62]. The midpoint-rooted tree was then visualized by iTOL (ver5.5.1; https://itol.embl.de/) phylogenetic tree visualization.

2.2. Prediction of pre-miRNAs by an ab initio approach

Vmir (an *ab initio* program) algorithm was used to predict pre-miRNAs of MERS-CoV, SARS-CoV and SARS-CoV-2 fasta sequences by setting strict cut-off parameters (minimal window count: 35, a hairpin length value: 50 to 220, and window size: 500 and step size: 1), as described by other literature [55,63–65]. The correspondences were then inputted to the miRNA fold algorithm as multi-fasta format for the strict-efficient prediction of hairpin structure [66], and further validated by ViralmiR, (a support vector machine) [67].

2.3. Secondary structure validation of putative miRNA candidates

The potential pre-miRNAs were submitted to Mfold (a web server algorithm) to predict the folding-back secondary structure by setting default parameters. The nucleotide length, (G + C) content and Minimal Folding Free Energy (MFE, ΔG kcal/mol) (cut-off value ≤ -20 kcal/mol) values were also fetched to calculate Minimal Folding Free Energy Index (MFEI) as discussed in literature by Zhang et al. [68].

2.4. Prediction of mature miRNAs, and phylogeny construction

MatureBayes, a Naïve Bayes classifier, was used to identify the potential mature miRNA:miRNA* duplexes from the predicted viral microRNA precursors [69], and extract the duplex 5′ stem mature miRNA like sequences because of their interaction with the 3′ UTR of human mRNAs [70,71]. Multiple sequence alignment of the miRNAs was performed using mafft –auto option (version 7.455) [60]. The phylogeny of the viral miRNAs was developed by PhyML (http://www.atgc-montpellier.fr/phyml/) [72]; using AIC (Akaike information criterion) for model selection. The midpoint-rooted trees were visualized by iTOL (ver5.5.1; https://itol.embl.de/).

2.5. Target prediction of viral miRNAs in human gene pools

miRDB, the Perl script implementing the MirTarget algorithm, was performed to predict potential targets in 3′-UTR or coding region of human mRNAs [73,74]. Mature miRNA transcripts were employed to the miRDB custom-target prediction to identify viral miRNAs targeting human genes.

2.6. GO and KEGG pathway analysis

Gene symbols and Uniprot gene IDs of the targeted genes were extracted from UniProtKB. Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG; https://www.genome.jp/kegg/) signaling pathway analyses were performed to extract the biological theme of the listed viral miRNA targeted human genes using the Database for Annotation, Visualization, and Integrated Discovery (DAVID) v6.8 (https://david.ncifcrf.gov/).

3. Result

Table 1 shows significant steps involved in the prediction of SARS-CoV-2 encoded miRNAs and its target in human, along with used bioinformatics tools and outputs.

3.1. Phylogenetic and sequences similarity analysis

In our study, we retrieved 206 SARS-CoV-2 genomes based on available data regarding different geographical locations (Asia, Europe, Africa, Australia, USA, Middle East), age groups in year (1-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 81-90, 91-100) and different periods (Jan–May 2020) (Supplementary file 1). To ensure a representative candidate we constructed phylogeny among all the retrieved genome sequences (Fig. 1). Though phylogenetic analysis revealed five different clusters (Fig. 1), we found that there are at least 99.6% sequence similarities with 53 mismatches at most among the sequences. Finally, the MT434792.1_SARS-CoV-2_human_USA NY-CDC-S was selected as a reference genome.

3.2. Prediction of pre-miRNAs by an ab initio approach

MERS-CoV, SARS-CoV, and SARS-CoV-2 genomes were searched in Vmir algorithm to predict the pre-miRNAs that resulted in 428 (Supplementary file 2), 137 (Supplementary file 3), and 158 (Supplementary file 4) potential findings respectively, and comparatively illustrated in Fig. 2 (B). Further evaluation was done using the miRNA fold and ViralmiR for proper hairpin structure. Predicted pre-miRNAs were finalized after scrutinizing in mfold software. All the pre-miRNAs have the Minimal Folding Free Energy of $\leq$ -20 kcal/mol, MFEI from 0.43 to 1.16 (average value 0.69), and the percentage of G + C content from 28.97% to 52% with an average of 39.64%.

Table 1
List of significant steps involved in the prediction of SARS-CoV-2 encoded miRNA like sequences and its human gene targets, along with used bioinformatics tools and outputs.

No	Steps	Used Bioinformatics tools or server	Outputs
1	Retrieval of genome sequences and construction of phylogenetic analysis	GISAID, NCBI, mafft –auto option (version 7.455), RAxML−V8.2.12, PartitionFinder−V2.1.1, and iTOL (ver5.5.1)	206 SARS-CoV-2 genomes
2	Prediction of the pre-miRNAs	Vmir algorithm(Cut-off values: minimal window count= 35, hairpin length value= 50–220, and window size= 500, and step size= 1)	158
3	Screening of the Vmir outputs of pre-miRNAs	miRNA fold algorithm	85
4	Screening of the miRNA fold outputs of pre-miRNAs	ViralmiR	85
5	Screening of the ViralmiR outputs of pre-miRNAs	Mfold web algorithm (MFE cut-off value $\leq$ -20 kcal/mol)	85
6	Extraction of potential mature miRNA like sequences from finalized pre-miRNAs	MatureBayes algorithm	85
7	Phylogenetic analysis of the miRNAs of MERS-CoV, SARS-CoV, and SARS-CoV-2	mafft –auto option (version 7.455), PhyML, and iTOL (ver5.5.1)	–
8	Prediction of human gene targets	miRDB Perl script (cut-off Target score= 100)	119
9	Functional annotation analysis	DAVID v6.8	–
10	Final number of viral miRNA candidates highlighted	–	8
11	Final number of human genes studied	–	14

3.3. Putative miRNA based phylogeny revealed three clusters of miRNAs

Analysis of the predicted pre-miRNA sequences in MatureBayes resulted in 402 (Supplementary file 2), 137 (Supplementary file 3), and 85 (Supplementary file 5) mature miRNAs of MERS-CoV, SARS-CoV and SARS-CoV-2 respectively. The phylogeny of the respective miRNAs revealed three major clusters (Fig. 3) named as Group-A, -B, and -C. Group-A is the largest group and consists of 249 miRNAs, where 34 of those belong to SARS-CoV-2. Group-B is the smallest group, containing 165 miRNAs. There are 23 miRNAs of SARS-CoV-2 in the second group. A total of 210 miRNAs are present in the Group-C, and 28 of those are from SARS-CoV-2.

3.4. Investigation of SARS-CoV-2 encoded mature miRNAs targets in human gene

We used SARS-CoV-2 encoded 85 miRNAs in miRDB for target prediction in humans. A total of 119 human genes are identified that seem to be targeted by 29 viral miRNAs (Supplementary Table 1). All targeted human genes have the target score of 100 that indicates maximum confidence in the prediction.

3.5. GO and KEGG pathway analysis

In our study, we used DAVID software to analyze the functional annotation of the viral miRNA-targeted human genes (the result is available in Supplementary file 6). Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway annotation and GO analysis were employed to identify the biological theme of the viral miRNAs targeting human genes. KEGG annotation analysis data identified that these miRNAs have influenced genes in the Thyroid hormone signaling pathway (6 genes), Hippo signaling pathway (6 genes), Renal cell carcinoma (4 genes), Pathways in cancer (7 genes), Proteoglycans in cancer (5 genes) and a number of other signaling pathways (Fig. 4). GO analysis found that SARS-CoV-2 miRNAs targeted human genes are significantly associated with 37 biological processes, eight cellular components, and 13 molecular functions based on the relative P values (Fig. 5). We attempted to validate our findings with the gene expression profile of COVID-19 patients from published literature (Table 2). We searched for alignments of predicted miRNA sequences in the raw RNA-seq dataset (GSE147507; https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE147507) of the transcriptional response to SARS-CoV-2 infection. An alignment search using the mature miRNA sequence was executed against RNA-seq data of SARS-CoV-2 infected primary human lung epithelium (NHBE) (SRX7990866), A549 (SRX7990875) and A549-ACE2 cells (SRX8089273) using Megablast (optimized for highly similar sequences). The search identified 100% alignment for SARS-CoV-2-miR-055, SARS-CoV-2-miR-058 and SARS-CoV-2-miR-084 miRNAs (E-value $<$0.001) against RNA-seq data of infected NHBE cell. Notably, each of the following 10 putative miRNAs: SARS-CoV-2-miR-005, SARS-CoV-2-miR-007, SARS-CoV-2-miR-027, SARS-CoV-2-miR-029, SARS-CoV-2-miR-055, SARS-CoV-2-miR-058, SARS-CoV-2-miR-060, SARS-CoV-2-miR-063, SARS-CoV-2-miR-077 and SARS-CoV-2-miR-084 also resulted in 100% match (E-value $\leq$0.001) against both the RNA-seq data of SARS-CoV-2 infected A549 and A549-ACE2 cell lines (Supplementary Table 2). Zhou et al. (2020) conducted metatranscriptomic sequencing to profile immune signatures in the bronchoalveolar lavage fluid (BALF) of eight COVID-19 cases [75]. The research group proposed some genes to be downregulated such as, *TBC1D4*, *CTNNB1*, *ADCY6*, *PLXNA4*, *POU2F2* and *ZFHX4* during the viral infection. Xiong et al. (2020) carried out transcriptome sequencing of the RNAs isolated from the BALF and peripheral blood mononuclear cells (PBMC) specimens of COVID-19 patients [76]. The study reported that *TGFB2* gene was significantly

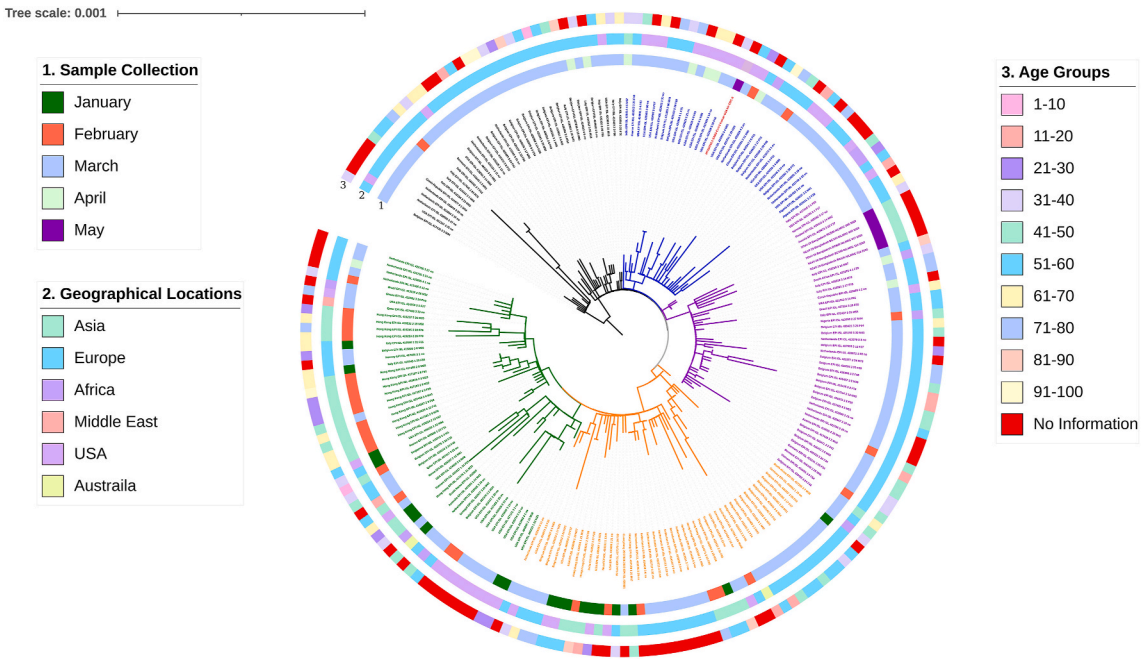

Fig. 1. Phylogeny of the retrieved 206 SARS-CoV-2 genomes. Five different clusters have been shown in different colors. The reference genome has been indicated by red color in the node. Months, geographical locations and age group variations are indicated.

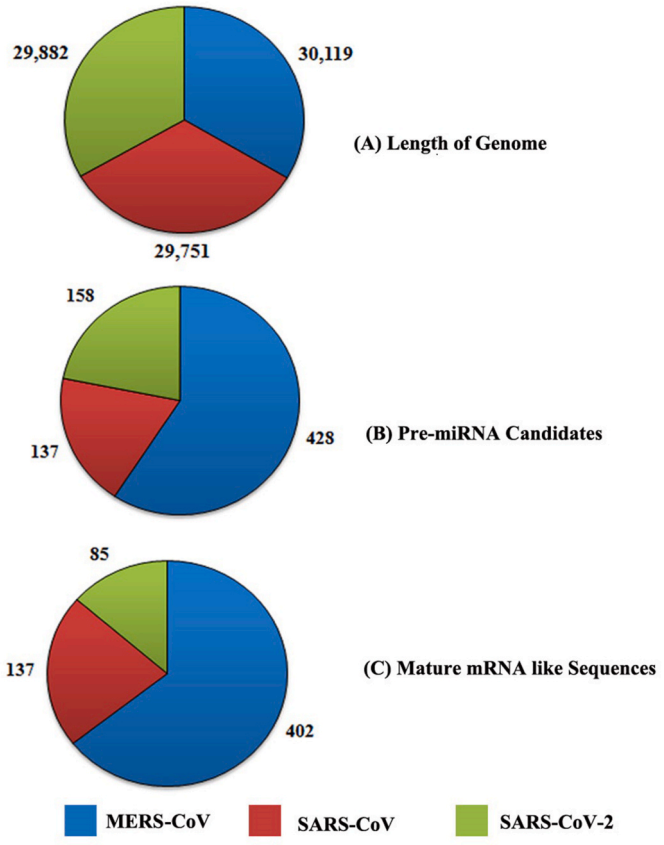

Fig. 2. Comparative representation of MERS-CoV, SARS-CoV, and SARS-CoV-2 based on (A) Length of the genome, (B) Pre-miRNA candidates, and (C) miRNA-like sequences.

overexpressed, which in turn, causes increased expression of TGF-b and that might be the causative factor for pulmonary fibrosis in SARS-CoV-2 infected patients. Evidently, the aforementioned genes targeted by the viral miRNAs in this *in silico* prediction signifies possible miRNA-mediated human gene expression. Finally, we emphasized on eight putative miRNAs targeting 14 human genes that are involved in the adaptive hypoxic response, neuroinvasion and hormonal regulation, and tumorigenic progression, and the findings were correlated with current clinical data in COVID-19 patient (Table 3).

4. Discussion

SARS-CoV-2 has unnerved the whole world with its catastrophic consequences. Although the viral pathogenesis is not fully understood, a crucial part of the infection is critically dependent on the host machinery by either using or manipulating it. There were speculations that RNA viruses are incapable of encoding miRNAs [30–32]. However, the discovery of host defense evasion in exploitation of host miRNA transcription machineries by SARS-CoV [77] might suggest the alternative which has led to the search of potential miRNA in the genome of SARS-CoV-2. Besides, viral miRNAs are known to notoriously manipulate both cellular and viral gene expression [29]. Within the scope of this computational study, we attempted to predict SARS-CoV-2 miRNA-host interactions, which might provide potential insights regarding underlying mechanism of the viral infection. In the present study, 206 SARS-CoV-2 genomes were employed for phylogeny study. Since there were more than 99% similarities among all the retrieved genomes, a specific genome of SARS-CoV-2 (MT434792.1) was prioritized for recognizing the putative miRNAs. We identified 402, 137, and 85 putative miRNAs for MERS-CoV, SARS-CoV, and SARS-CoV-2, respectively, for phylogenetic analysis.

MERS-CoV, SARS-CoV and SARS-CoV-2 belong to the Coronaviridae family, mostly involved with respiratory disorders. We developed the midpoint-rooted tree of the miRNA sequences to ensure the same rate of evolution of the viral encoded miRNAs. Though the sequence-based phylogeny of the miRNAs has limited utility, the miRNA sequences are of high utility in quantitative phylogenetic study [78]. The present study revealed the MERS-CoV encoded miRNA (MERS-CoV-mir-055) as the

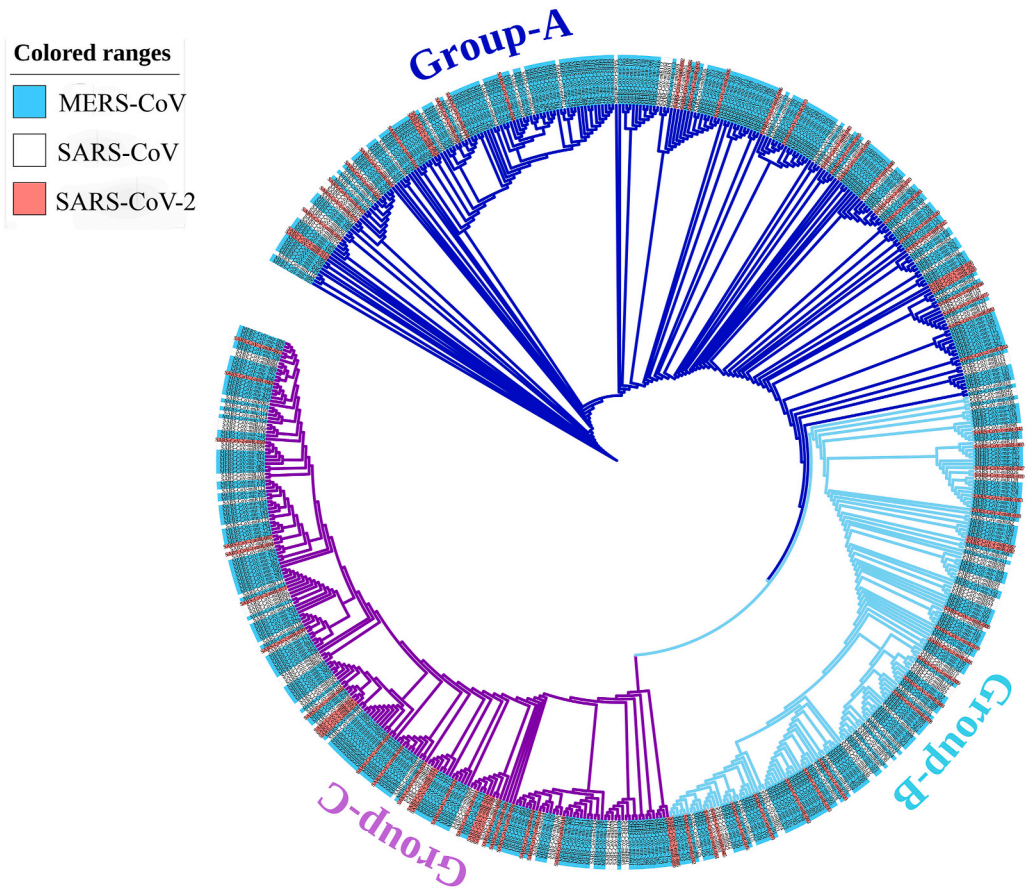

Fig. 3. Phylogenetic tree (unrooted) of the miRNAs of SARS-CoV, MERS-CoV, and SARS-CoV-2: Group-A, -B, and -C have been indicated by navy blue, sky blue, and purple color.

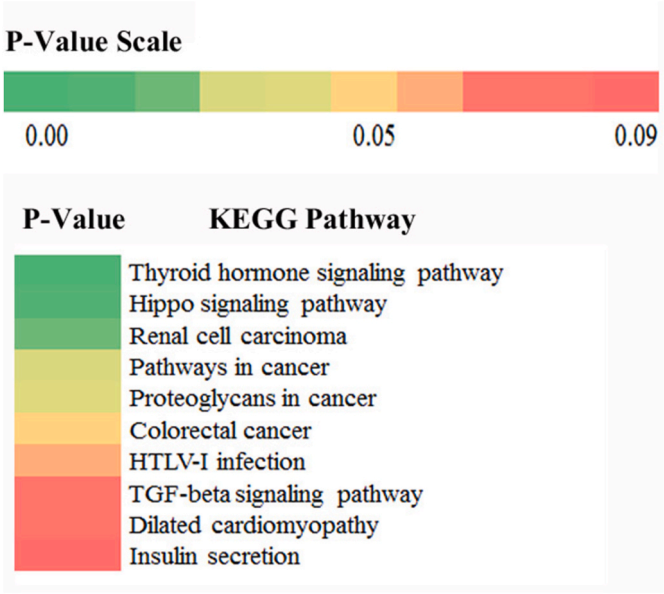

Fig. 4. Different KEGG pathways involvement by target genes according to DAVID analysis.

ancestral miRNA of all the miRNAs selected for the study. All the miRNAs of SARS-CoV-2 form cluster with the miRNAs of either SARS-CoV or MERS-CoV. The sequence based phylogenetic tree represents short branch length in all but two miRNAs (Figure not shown), one belongs to SARS-CoV miRNA (mir-013) and another to MERS-CoV miRNA (mir-319). SARS-CoV-mir-013 with large branch length falls in the group A, which forms cluster with another miRNA of SARS-CoV and MERS-CoV-mir-413 with a very low bootstrap value (<50). Again, MERS-CoV-mir-319 with larger branch is present within a very small sub-clade of group-C that contains only three miRNA of MERS-CoV and the bootstrap value is > 65. Longer branch length reflects more genetic divergence, thus it is expected that these two viruses have undergone several mutational changes during the course of evolution and this might occur due to the loss or gain of the exon, intron or flanking regions of the miRNAs [78]. This is however, contradictory with the fact that miRNAs are inferred as the rare genomic changes in most of the organisms. Again, as the SARS-CoV-2 has higher mutation ability, it could be expected that the miRNAs of this virus might have also adopted this ability of high rate of mutation, though in our study, we did not observe such divergence within the miRNA sequences of SARS-CoV-2. In fact, the smaller branches strictly support the origin of these miRNAs from conserved genomic regions. One limitation of this study is that we did not look for the intron or exon region or even the flanking regions of the miRNAs, which might provide us more information about the evolutionary pattern of these miRNAs of the three virus species [78]. Later, we looked for the eight putative miRNAs of the SARS-CoV-2 that might target 14 human genes. These eight miRNAs of SARS-CoV-2 are randomly distributed within the three classes, among which SARS-CoV-2-miR-029 and SARS-CoV-2-miR-055 belong to group-A; SARS-CoV-2-miR-084, SARS-CoV-2-miR-027 and SARS-CoV-2-miR-005 belong to group-B, and SARS-CoV-2-miR-077, SARS-CoV-2-miR-060 and SARS-CoV-2-miR-007 belong to group-C.

Initially, we predicted 85 miRNAs from 158 pre-miRNAs encoded by SARS-CoV-2. Analyzing miRNA target prediction, we extracted 119

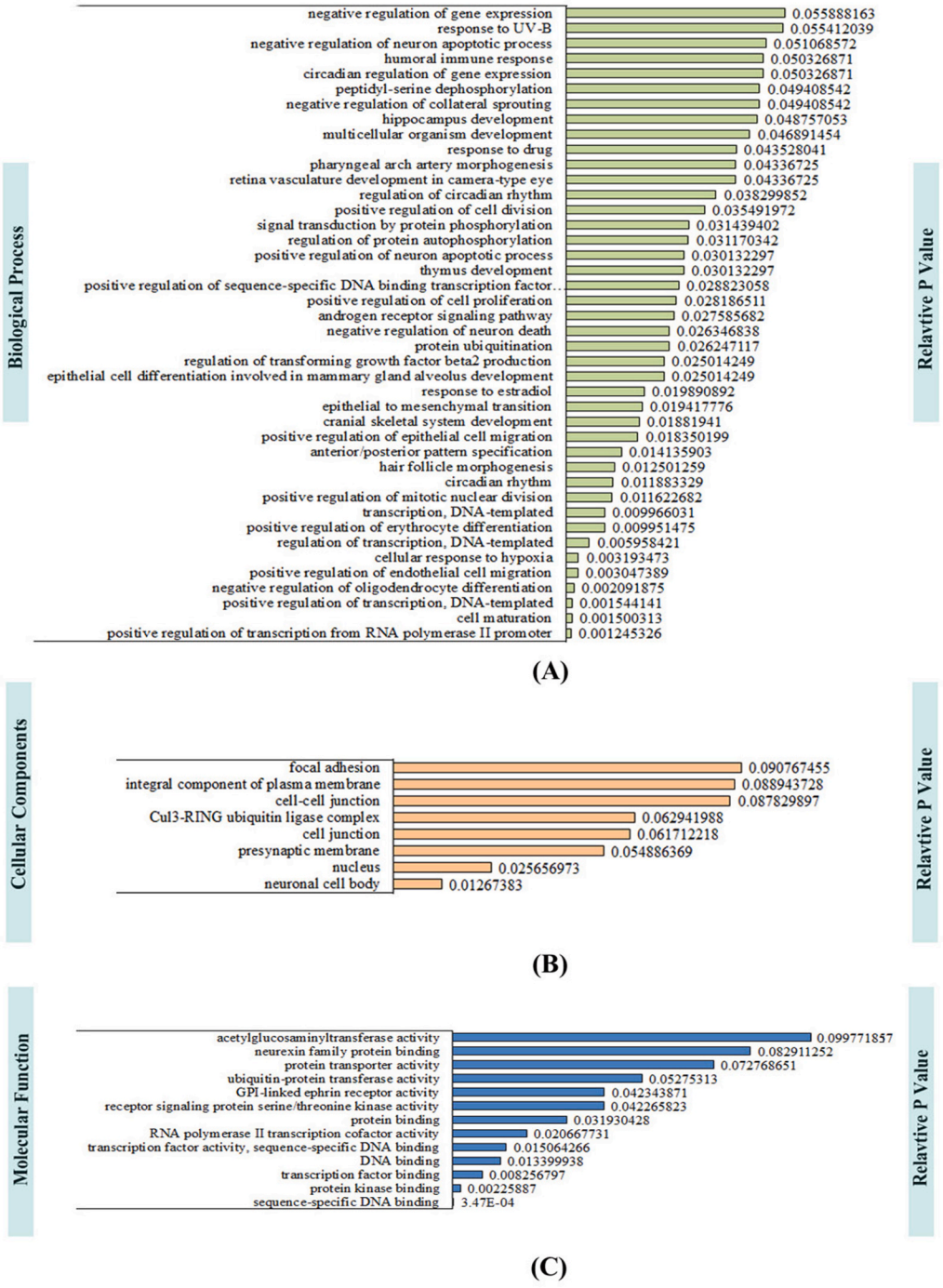

Fig. 5. Gene Ontology Classification based on DAVID analysis: The terms were summarized in three categories: (A) Biological Process, (B) Cellular Component, and (C) Molecular Component.

human genes having a target score of 100 targeted by 29 viral miRNAs out of 85. Finally, we highlighted eight miRNAs that could influence over 14 genes involved in the adaptive hypoxic response, neuroinvasion, endocrine homeostasis and tumorigenic progression in COVID-19 patients.

Among the predicted miRNA-targeted human genes in this study, *HIF1A* is involved with the regulation of several processes, including gene expression, transcription, cellular differentiation, transition and migration, response to hypoxia and interleukins, *TGFB2* production, angiogenesis via *p300/CBP* modulation. SARS-CoV-2 induced cytokine and chemokine storm cause alveolar and capillary endothelial damage leading to microvascular leaks [79–81]. Resultant cell injury may trigger coagulation cascades to cause thrombosis and organ ischaemia [82]. Simultaneously, loss of alveolar gaseous exchange and ventilation-perfusion mismatch incites hypoxia [83,84]. Although normoxia fundamentally represses hypoxia-inducible factor-1 (*HIF-1*) alpha subunit, it is upregulated in such hypoxic conditions to form heterodimeric *HIF-1*, a master orchestrator of cellular response to hypoxia [85]. Stabilization of *HIF1A* may lead to transcription of factors linked with new blood vessel formation, invasion, and metastasis as previous studies suggest [86–88]. *HIF1A* accumulation and activation of *HIF* complex alter angiogenesis via several genes including *VEGF*, *Ang-2*, *SDF-1*, *MMPsA* [89]. A study analyzing autopsied lung specimens from COVID-19 patients found high amount of new vessel growth (2.7 times

Table 2
Validation of the predicted viral miRNAs in the present study with the gene expression profile of COVID-19 patients from published literature.

Predicted miRNA	Predicted miRNA Nucleotide Sequences	Gene Symbol	*Gene Expression Profile of COVID-19 Patients from Published Literature*	Gene Specific Function
SARS-CoV-2-miR-084	UUGUUGUUGGCCUUUACCAGAC	*TGFB2*	Overexpression [76]	• Negative regulation of cell population proliferation (GO:0008285) • Positive regulation of cell population proliferation (GO:0008284) • Positive regulation of epithelial to mesenchymal transition (GO:0010936)
SARS-CoV-2-miR-063	CCAUUUUUCUAAAACCACUCUG	*TBC1D4*	Downregulation [75]	• Cellular response to insulin stimulus (GO:0032869)
SARS-CoV-2-miR-060	UCUUAAAAGAGGGUGUGUAGUG	*CTNNB1*	Downregulation [75]	• Negative regulation of cell population proliferation (GO:0008285) • Positive regulation of cell population proliferation (GO:0008284)
SARS-CoV-2-miR-058	GUUGGCACUUUUCUCAAAGCUU	*ADCY6*	Downregulation [75]	• Negative correlation with immune process- related signaling pathways [159]
SARS-CoV-2-miR-029	AUGCAAAAGUAUUCUACACUCC	*PLXNA4*	Downregulation [75]	• Facial nerve morphogenesis (GO:0021610) • Facial nerve structural organization (GO:0021612) • Glossopharyngeal nerve morphogenesis (GO:0021615)
SARS-CoV-2-miR-007	UUUUUGGCUUUGUGUGCUGACU	*POU2F2*	Downregulation [75]	• Sequence-specific DNA binding (GO:0043565) • Humoral immune response (GO:0006959)
SARS-CoV-2-miR-007	UUUUUGGCUUUGUGUGCUGACU	*ZFHX4*	Downregulation [75]	• Positive regulation of DNA-templated transcription (GO:0006355)

Table 3
Lists of human genes targeted by SARS-CoV-2 encoded miRNAs and their particular function of interest.

Predicted miRNA sequences	Name of miRNA	Gene Symbol (UniProtKB ID)	Gene description	Proposed functions highlighted in this study
AAAAAAGGUGCCUGGAAUAUUG	SARS-CoV-2-miR-005	*HIF1A* (Q16665)	Hypoxia-inducible factor 1-alpha	Transcriptional regulator of the adaptive response to hypoxia, Tumorigenesis and metastasis
UUUUUGGCUUUGUGUGCUGACU	SARS-CoV-2-miR-007	*GHR* (P10912)	Growth hormone receptor	Endocrine homeostasis
CAAUAACAGUUACACCGGAAGC	SARS-CoV-2-miR-027	*DLX1* (P56177)	Homeobox protein DLX-1	Neuroinvasion
AUGCAAAAGUAUUCUACACUCC	SARS-CoV-2-miR-029	*ESR1* (P03372)	Estrogen receptor 1	Endocrine homeostasis
CAAAGUUUUUAUGACAGCAUCU	SARS-CoV-2-miR-055	*MED14* (O60244)	Mediator of RNA polymerase II transcription subunit 14	Endocrine homeostasis
UCUUAAAAGAGGGUGUGUAGUG	SARS-CoV-2-miR-060	*BCL2* (P10415)	Apoptosis regulator Bcl-2	Tumorigenesis
		CTNNB1(P35222)	Catenin beta-1	Tumorigenesis, Endocrine homeostasis Neuroinvasion
		ETS1 (P14921)	ETS proto-oncogene 1, transcription factor	Tumorigenesis, Endocrine homeostasis
AGUGUGCUUUUCCAUCAUGACA	SARS-CoV-2-miR-077	*IGF2* (A0A2R8Y747)	Insulin-like growth factor II	Tumorigenesis
UUGUUGUUGGCCUUUACCAGAC	SARS-CoV-2-miR-084	*CRKL* (P46109)	CRK like proto-oncogene, adaptor protein	Tumorigenesis
		ID2 (Q02363)	Inhibitor of DNA binding 2	Neuroinvasion
		PPARGC1A (Q9UBK2)	Peroxisome proliferator-activated receptor gamma coactivator 1-alpha	Neuroinvasion, Endocrine homeostasis
		PROKR2 (Q8NFJ6)	Prokineticin receptor 2	Neuroinvasion
		TGFB2 (P61812)	Transforming growth factor beta-2 proprotein	Tumorigenesis and metastasis

higher than influenza-infected lungs) mainly through a mechanism of intussusceptive angiogenesis, which could be attributed to an over-expression of *HIF1A* [90]. According to protein interaction analysis in this study, *HIF1A* interacts with *GATA* and *GATA1* transcription factors that play pivotal role in erythroid development by regulating the transformation of fetal hemoglobin to adult hemoglobin [91]. *GATA1* activates transcription of the erythropoietin (EPO) receptor, essential for normal erythropoiesis through EPO signaling [92,93]. Both *in-silico* and lab studies have validated *HIF1* induced human *GATA1* gene expression to promote hypoxia-induced erythroid differentiation [94,95]. Reports of decreased red blood cell count [96–98] and low hemoglobin levels [99,100] in COVID-19 patients had propagated interest in recombinant EPO (rtEPO) therapy for the recovery of affected patients, which later translated into the demonstration of promising results in the prognosis of COVID-19 [101,102]. However, arterial oxygen saturation progressively drops in some patients with only a minute increase in tidal volume, a clinical phenomenon that has been coined as 'happy hypoxia' [103,104], which could develop due to a decline in the oxygen-carrying capacity in blood coupled with a seeming disruption of respiratory compensation for acute hypoxia [105,106].

We have found that viral miRNAs target the *BCL2* and *PPARGC1A* host genes, involved in downregulation of neuronal apoptosis and neuron death in the host. The induction of apoptosis is a host antiviral response to limit viral load [107]. Viruses try to overthrow apoptotic host defense by chalking out strategies to either encode for viral proteins that mimic or regulate pro-apoptotic homologues through other molecular pathways [108–112]. Peroxisome proliferator-activated receptor-gamma (*PPAR-γ*) coactivator 1-alpha (*PPARGC1A*) is a *PPAR-γ* coactivator, and master regulator of mitochondrial biogenesis in multiple cell lines [113–116]. Cellular oxidative stress upregulates

PPARGC1A that encodes a transcriptional co-activator implicated in neurodegenerative disorders [117,118]. Coronaviruses can gain entry into the central nervous system (CNS) through a synapse-mediated route [119,120]. There are reports of SARS-CoV neuroinvasion in both humans and experimental animals [121–123]. SARS-CoV-2 has been isolated in the cerebrospinal fluid of some COVID-19 patients [124]. Viral protein-mediated disruptions of the respiratory center in the brainstem could also elucidate respiratory malfunctions in COVID-19 patients [125]. Besides, vagal receptors project afferent nerves from lungs to the brain, the inputs of which could be significant in shaping the pattern of breathing, sense of dyspnea in some patients and loss of involuntary over-breathing in silent hypoxaemic patients [106,126]. In this study, viral miRNAs target *DLX1*, *ID2*, and *CTNNB1* genes linked with the negative regulation of oligodendrocyte differentiation. Oligodendrocytes are known to be responsible for myelination in the central nervous system [127]. *DLX1* is responsible for the differentiation and survival of inhibitory neurons in the forebrain [128]. Targeting genes that modulate oligodendrocyte differentiation might provide a molecular basis of SARS-CoV-2 viral neuroinvasion and predict potential neurogenic pathogenicity by demyelination of nerves. We have identified four genes that control circadian rhythm of which *PROKR2* and *PPARGC1A* are of particular interest. *PROKR2* gene encodes for a protein called Prokineticin Receptor 2, and an interplay of the ligand-receptor is crucial in the development of olfactory neurons that migrate from nose to the olfactory bulb in forebrain, which is critical for the perception of odors [129]. Loss of sense of smell and taste in a wide range of otherwise asymptomatic patients had previously given rise to the conjecture that SARS-CoV-2 might target CNS through olfactory bulb and invade the olfactory nerve [130]. *PROKR2* gene could be a potential target for SARS-CoV-2 viral miRNA and may have some role in the development of anosmia in COVID-19 patients [131]. *ETS1*, *ESR1*, *GHR*, *CTNNB1* genes are involved in the biological response to estradiol whereas, another triad of identified genes *MED14*, *PPARCG1A*, *CTNNB1* modulates androgen receptor signaling pathway. Endocrine homeostasis of gonadal steroids, cortisol, prolactin, thyroid hormone, and growth hormone (GH) depends on circadian rhythm, which, if dysregulated, may throw off physiological hormonal balance [132]. However, the *PPARGC1A* gene may have a unique role in estrogen signaling. In vivo studies have backed *PPARGC1A* as a powerful regulator of *VEGF* expression and angiogenesis by bona fide co-activation of orphan nuclear receptor *ERR-α* (estrogen-related receptor-alpha) dependent transcriptional activity [133,134]. Sex steroid 17β-estradiol (E2) upon stimulation acts directly on the endothelium and positively impacts vascular functions [135–138]. Increasing response to estradiol and modulation of androgen receptor pathway can be clinically beneficial in COVID-19 patients by silencing inflammatory reactions, modulating innate and adaptive immune responses, regenerating damaged lung capillary endothelium, and repair of tissues [139]. These counterbalancing measures are of significance since infection, injury and chronic inflammation, if not contained, may lead to carcinogenesis by expediting proliferation, survival and migration [140].

Death in patients with COVID-19 is associated with age, gender, and comorbidities [141]. Besides, those who recover may have to deal with future clinical consequences of which, cancer can be a particular concern [142]. It is thought-provoking whether COVID-19 can set towards tumorigenesis via a complex dysregulation of the oncogenes-miRNA-tumor suppressor genes (*TSGs*) network, induced by some genetic and epigenetic factors [143]. KEGG pathway analysis in this study has identified *HIF1A*, *TGFB2*, *ETS1*, *CTNNB1*, *IGF2*, *CRKL*, *BCL2* genes to have regulatory roles in constituting proteoglycans, activating pathways in cancer, involvement in colorectal and renal cell carcinoma. COVID-19 hypoxia creates an interior milieu that can favor *HIF1A* driven *HIF* cell signaling involved in blood vessel formation, epithelial to mesenchymal transition, cell mobility, and metastasis [144–147]. Defects in *TGFB2* and *ETS1* pathways can lead to the opening of multiple oncogenic pathways, such as evasion of host immune surveillance, stem cell development, sustained angiogenesis, and loss of apoptotic control, aberrant cellular proliferation, epithelial-to-mesenchymal transition, and metastasis [148–151]. Mutations of *CTNNB1* genes alter the typical 3D structure of the β-catenin protein, leading to uncontrolled cell proliferation, immunosuppression, disrupted metabolic regulation [152]. Previous studies have associated the role of *CRKL* in epithelial cell migration and invasion to aid in metastasis [153,154]. Elevated *IGF2* expression has a propensity for heightening the risk of developing breast, prostate, lung, and colorectal cancers [155,156]. Deregulation of *BCL2* expression deviates mitochondrial apoptotic machinery to cause tumorigenesis and therapeutic resistance in several human malignancies [157,158]. In the context of COVID-19, a complex interplay between these genes, viral miRNAs coupled with environmental factors and host defenses, could potentially initiate tumorigenesis in an infected patient. However, whether or to what extent SARS-CoV-2 viral miRNAs have involvement in the development and progression of tumor and cancer in human hosts by misexpression of some vital regulators is a matter best left for future genomic and experimental studies to validate.

5. Conclusion

Since the onset of COVID-19, viral miRNAs have gained extensive focus in unraveling biological activities associated with host-virus interactions. This study predicts several putative viral miRNAs from SARS-CoV-2 genome targeting a number of human genes. Additionally, possible regulatory roles of the predicted miRNAs in adaptive hypoxic response, neuroinvasion, hormonal imbalance, and activation of cancer pathways are constructed in light of SARS-CoV-2 encoded miRNA mediated host gene expression. Future laboratory validation and confirmation of our findings will add newer dimensions to host-virus interaction and help develop potential therapeutics against SARS-CoV-2.

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Author's contributions

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Data availability

All data generated and analyzed during this study are included in the main manuscript or supplementary files.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.compbiomed.2021.104451.

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