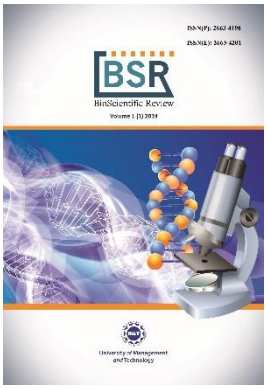


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# *In silico* Analysis of Human miRNAs in SARS-CoV-2 Genome

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**Abstract**

In December 2019, a new coronavirus (SARS-CoV-2) was discovered in Wuhan (China) that was rapidly transmitted to many other countries. Henceforth, the World Health Organization (WHO) Emergency Committee declared a global health emergency on January 30, 2020. Statistics depicted the fatality rate as about 1.4%. In this study, a potential antiviral treatment for the SARS-CoV-2 virus using host miRNAs was explored which may slow down the expression of viral genes to suppress viral replication. The miRNAs from genome (coronavirus / SARS-CoV-2) were analyzed using various computational approaches. The complete genome sequence was retrieved from NCBI. The result of our study highlighted that hsa-miR-3675-3p (MD19), hsa-miR-363-5p (MD220), hsa-miR-325 (MD306), hsa-miR-2114-5p (MD306), hsa-miR-744-3p (MR186) and hsa-miR-448 (MR186) can be used as an antiviral treatment to quell the replication of SARS-CoV-2 virus in human beings. The findings and observations of our study opened new possibilities to explore both the pathogenesis function of miRNAs and for the development of novel antiviral drugs.

## 1. Introduction

In December 2019, a new coronavirus (SARS-CoV-2) emerged in Wuhan (China) and rapidly spread to many other countries [1–3]. The World Health Organization (WHO) Emergency Committee declared a global health emergency on Jan. 30, 2020, based on growing case rates. As of 24 April 2020, 177,108,695 individuals were infected by SARS-CoV-2 worldwide and 3,840,223 people died because of it. As of 19 June 2021, a total of 2,412,226,768 vaccine doses have been administered, worldwide [4]. SARS-CoV-2 is listed as a top category pathogen by several organizations including WHO, CDC and NIH because its fatality rate is up to 1.4% [5–7]. Clinical signs of SARS-CoV-2 closely resemble those seen in MERS and SARS infections [8, 9]. A recent report [10] indicated that the potential source(s) has not been identified yet which caused the transmission of the virus to human beings.

Coronaviruses have a monopartite plus-strand RNA genome and belong to the *Coronaviridae*, often pleiomorphic virions, with a diameter of approximately 80 to 120 nm [5]. Coronaviruses contain a positive, capped and polyadenylated RNA strand with the largest genomic RNA (approximately 27 – 32 kb) in size that causes respiratory, gastrointestinal, hepatic, and neurologic diseases in human beings and animals [5, 11, 12]. The “N”

protein was found to be bound to viral RNA and packaged into ribonucleoprotein complexes, which are located at the viral membrane's internal face [13]. Coronaviruses have at least three viral proteins in their membrane including a) Spike (S), which reveals the structure of the virus as a crown; b) membrane protein (M), coated three times and provided with a small N-terminal ecto-domain; and c) a hydrophobic protein, that is, a cytoplasmic tail and a small membrane protein (E) [14, 15]. So far, the presence of coronaviruses has been identified in mice, rats, pigs, cats, rabbits, horses and livestock, causing a number of serious diseases including gastroenteritis and respiratory tract problems [16].

MicroRNAs (miRNAs) are single stranded RNAs (ssRNAs), around 18 – 25 nucleotides long that modulate protein-coding genes [17, 18]. Introns of protein coding genes, UTR of protein coding genes, exons of non-coding genes, and introns of non-coding genes are all sites where miRNAs can be found [19, 20]. It is well documented that miRNAs perform different biological or physiological functions including apoptosis, development, tumorigenesis, stress response, proliferation and fat metabolism [21, 22]. RNA polymerase II are generally used to make miRNAs [23]. Main Drosha converts the main transcript into a hairpin pre-miRNA using RNase III enzyme along with the dsRNA binding protein [24, 25], exporting 5/Ran-GTP transport to the nuclear pre-miRNA, which is then cleaved by the cytoplasmic RNase III Dicer to create an incomplete 21 – 25 nucleotide dsRNA [26, 27]. In the RNA Induced Silencing Complex (RISC), a strand known as the mature miRNA strand is loaded and RISC is guided to target it where it hybridizes with complementary sequences, causing cleavage or translational inhibition. The presence of viral miRNA is associated with the role of virus infection, as indicated by numerous researches. Additionally, emerging evidence has confirmed the connection of viral miRNAs with human diseases [28, 29].

Viral miRNAs were found to alter the life cycle of a virus and also affect its survival in hosts [30, 31]. Significantly, viral miRNAs can target not only the virus but also the host's miRNA regulation. Identifying viral miRNAs using bioinformatics technologies and techniques is, therefore, an evolving approach to explore the mechanisms of virus-host interaction [30, 32].

In this study, we utilized various computational methods and techniques including the RNA-hybridization technique to identify the potential targets of human microRNAs of the SARS-CoV-2 genome. This study aids in enhancing the understanding of host-pathogen interactions as well as the development of new antiviral therapies for all SARS-CoV-2 strains.

## 2. Materials and Methods

### 2.1. Data Retrieval

The complete SARS-CoV-2 genome sequence was obtained from the National Center for Biotechnology Information (NCBI) (Isolate: Wuhan-Hu-1, NCBI Reference Sequence: NC_045512.2) and used for miRNA prediction. Figure 1 shows the overall workflow used in this study. Complete genome isolate from Wuhan-Hu-1, revised by authors on 30 March 2020, contains 29903 bp ss-RNA.

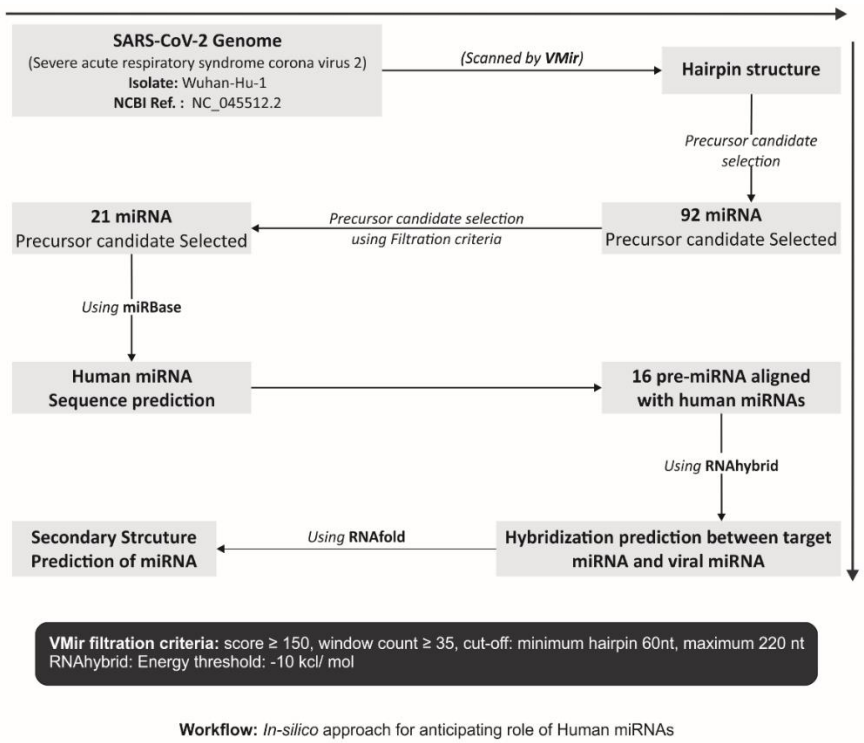


**Figure 1.** Human miRNA prediction of SARS-CoV-2 workflow (Isolate Wuhan-Hu-1)

### 2.2. Hairpin-structured miRNA Precursors Prediction – Pre-miRNA Extraction

A flowchart (Figure 1) describes the computational prediction of miRNA precursors. In our study, VMir Analyzer tool was used to search the genome for experimentally confirmed hairpin-structure miRNAs precursor [33-35]. Predictions for VMir were performed using default parameters. For further investigation, pre-miRNAs having a VMir score of less than and equal to 150 (Window Count, WC = 35) were chosen. VMir Viewer was used for the visualization of scanned hairpins [35, 36, 37].

### 2.3. Human miRNAs Sequence Prediction

The miRbase database contains the sequences of human miRNAs (http://www.mirbase.org/search.shtml) [38]. The genome nucleotide segment under analysis was scanned using the VMir tool and each segment's input and nucleotide similarity to all human microRNAs was extensively analyzed using blast program in miRbase search tool.

### 2.4. Hybridization Prediction between Target miRNA and Viral miRNA

RNAhybrid predicts miRNA based on the minimum free energy and site complementarity. RNAhybrid is also used in viral genome to locate the exact match for miRNA target [39]. RNAhybrid (httpss://bibiserv.cebitec.uni-bielefeld.de/rnahybrid) was utilized to evaluate miRNAs against SARS-CoV-2 genome attachment at an energy threshold of -10 kcl/ mol and other filters were set to default parameters. The tool identified some minimum free energy miRNA precursors that deviated from the threshold values, so these were removed from the final list. RNAhybrid's result was

categorized in terms of pairing energy and pattern hybridization.

### 2.5. Secondary Structure Prediction of miRNA

The structure of pre-miRNAs was predicted using the online server "RNAfold" with default parameters (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi) [40].

## 3. Results

### 3.1. miRNA Precursor (Pre-miRNA) Hairpins Prediction

The viral genome was screened and visualized using VMIR Analyzer and VMIR Viewer, respectively. VMIR Viewer displays the entire output graphically, including the sequence score and length. Figure 2 illustrates the visual representation of miRNA hairpin precursor of SARS-CoV-2 genome. We filtered 92 candidate hairpins through the default parameters of VMir Analyzer tool as shown in Figure 2(a). A filter using specific parameters and custom configuration, that is, for minimum hairpin score of 150, minimum window count of 35, a minimum cut-off value of 60 nt for hairpin size, and a maximum hairpin size of 220 nt was applied to avoid the bona fide candidate hairpin. Finally, for further study, 21 pre-miRNA hairpins were chosen as candidate hairpins (Figure 2).

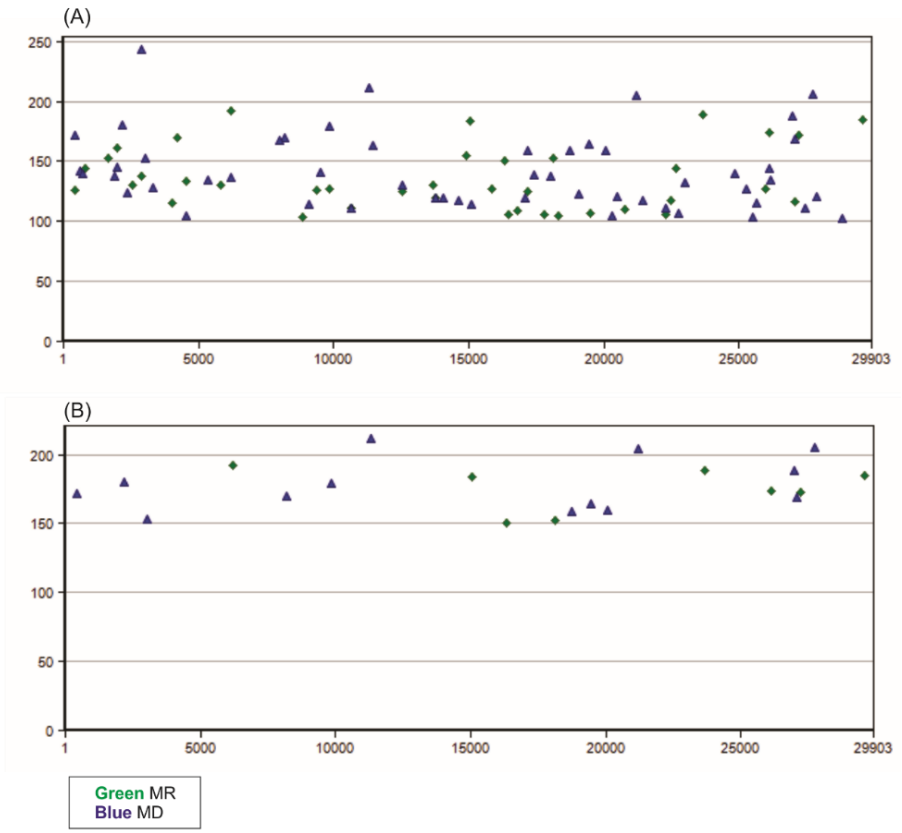


**Figure 2.** VMir analysis of SARS-CoV-2 genome is represented graphically (A) default setting was used to display all pre-miRNA hairpins (B) representation of predicated pre-miRNA after filtration

### 3.2. Human miRNAs Prediction from miRNAs Precursor (Hairpin)

The nucleotide similarity of 21 candidate miRNAs, precursors to human miRNAs, was searched using miRBase database (http://www.mirbase.org/search.shtml) (Table 1). Based on the considerable sequence similarities with human miRNAs, 16 precursors were selected as probable miRNA precursor candidates. Human miRNAs were identified as the primary target miRNAs with a similarity of at least 10 bp sequence with candidate miRNA precursors. Then, in the candidate miRNA precursors' 3' untranslated region, near or almost perfect alignment of all those miRNAs' seed areas (2 – 8) were possible miRNA targets. Perfect complementary matching between 3' untranslated region (UTR) of miRNA and the seed region of miRNA is essential for the fruitful cleavage of miRNA or translational repression. Viral precursors miRNA hairpins MD3, MD19, MD29, MD134, MD220, MD228, MD240, MD306, MD307, MD311, MR155, MR165, MR186, MR243, MR274, MR304 showed a significant similarity with hsa-miR-4471, hsa-miR-3675-3p, (hsa-miR-383-5p and hsa-miR-5197-3p), hsa-miR-190b-5p, hsa-miR-363-5p, hsa-miR-4802-3p, hsa-miR-23b-5p, (hsa-miR-325 and hsa-miR-2114-5p), (hsa-miR-215-3p, hsa-miR-548y, hsa-miR-338-3p and hsa-miR-3065-5p), hsa-miR-4699-3p and hsa-miR-6739-3p), hsa-miR-363-5p, hsa-miR-153-5p, (hsa-miR-744-3p, hsa-miR-4420 and hsa-miR-448), hsa-miR-4796-5p, hsa-miR-6867-5p, (hsa-miR-3064-5p and hsa-miR-411-5p), respectively.

**Table 1.** miRNAs Hairpin Precursor Sequence and Human miRNAs

| S. No | Hairpin | Score | Alignment (SARS-CoV-2 and Human microRNA) |
|---|---|---|---|
| 1 | MD3 | 62 | UserSeq 24 cuuaguagaaguugaa 39<br>hsa-miR-4471 7 cuuaguagagguuuaa 22 |
| 2 | MD19 | 62 | UserSeq 77 gaguuucuuagagacg 92<br>hsa-miR-3675-3p 16 gaguuccuuagagaug 1 |
| 3 | MD29 | 70 | UserSeq 81 agaaggugauugug 94<br>hsa-miR-383-5p 6 agaaggugauugug 19 |
| | | 70 | UserSeq 98 aagaagaguuugagccaucaacu 120<br>hsa-miR-5197-3p 1 aagaagagacugagucaucgaau 23 |
| 4 | MD134 | 69 | UserSeq 34 gauaugguugauacuaguuug 54<br>hsa-miR-190b-5p 2 gauauguuugauauuggguug 22 |
| 5 | MD220 | 65 | UserSeq 30 cguguauaacacguugcaauuu 51<br>hsa-miR-363-5p 1 cggguggaucacgaugcaauuu 22 |
| 6 | MD228 | 63 | UserSeq 62 uuaaagguuuacaaccau 79<br>hsa-miR-4802-3p 21 uugaagguuuccauccau 4 |
| 7 | MD240 | 63 | UserSeq 50 uucuuggaaugcugaucu 67<br>hsa-miR-23b-5p 5 uuccuggcaugcugauuu 22 |

| S. No | Hairpin | Score | Alignment (SARS-CoV-2 and Human microRNA) |
|---|---|---|---|
| 8 | MD306 | 68 | UserSeq 60 uugcuggacaccaucuagg 78<br>\|\| \|\|\|\|\|\|\|\| \|\|\|\|\|<br>hsa-miR-325 19 uuacuggacaccuacuagg 1 |
| | | 63 | UserSeq 1 accgcuucuagaaaguga 18<br>\|\|\|\|\|\|\| \|\| \|\|\| \|\|<br>hsa-miR-2114-5p 21 accgcuucaaggaaggga 4 |
| 9 | MD307 | 67 | UserSeq 20 gccuaaagaaaucacug 36<br>\|\|\|\|\|\|\|\|\|\|\| \|\| \|<br>hsa-miR-215-3p 18 gccuaaagaaaugacag 2 |
| | | 66 | UserSeq 24 aaagaaaucacuguu 38<br>\|\|\|\| \|\|\|\|\|\|\|\|<br>hsa-miR-548y 2 aaaguaaucacuguu 16 |
| | | 63 | UserSeq 24 aaagaaaucacuguugcu 41<br>\|\| \|\|\|\|\|\|\|\| \|\|\|\|<br>hsa-miR-338-3p 21 aacaaaaucacugaugcu 4 |
| | | 63 | UserSeq 24 aaagaaaucacuguugcu 41<br>\|\| \|\|\|\|\|\|\|\| \|\|\|\|<br>hsa-miR-3065-5p 3 aacaaaaucacugaugcu 20 |
| 10 | MD311 | 63 | UserSeq 13 acuuuacucuccaauuuu 30<br>\| \|\|\|\|\|\|\| \|\|\|\| \|\|<br>hsa-miR-4699-3p 1 aauuuacucugcaaucuu 18 |
| | | 62 | UserSeq 80 agaaagacagaaugau 95<br>\|\|\|\|\|\|\|\|\|\| \|\|<br>hsa-miR-6739-3p 16 agaaagacagaacaau 1 |
| 11 | MR155 | 68 | UserSeq 60 aaagugcaucuugauccuc 78<br>\|\|\| \|\|\|\|\| \|\|\|\|\| \|<br>hsa-miR-363-5p 22 aaauugcaucgugauccac 4 |
| 12 | MR165 | 67 | UserSeq 37 uaauuuaugugauguug 53<br>\| \|\|\|\| \|\|\|\|\|\|\|\|<br>hsa-miR-153-5p 1 ucauuuuugugauguug 17 |
| | | 63 | UserSeq 50 uugaauuuagugucaaca 67<br>\|\|\|\| \|\|\|\|\| \|\|\|\|<br>hsa-miR-744-3p 19 uugagguuaguggcaaca 2 |
| 13 | MR186 | 63 | UserSeq 66 cacugaggugugguaggug 83<br>\|\|\|\|\|\| \|\| \|\|\|\|\| \|\|<br>hsa-miR-4420 3 cacugaugucuguagcug 20 |
| | | 62 | UserSeq 82 ugccuguguaggaugu 97<br>\|\|\| \| \|\|\|\|\|\|\|\|<br>hsa-miR-448 2 ugcauauguaggaugu 17 |
| 14 | MR243 | 68 | UserSeq 52 aagugacauaguguaggca 70<br>\|\|\|\|\|\|\|\| \|\|\| \|\|\| \|\|<br>hsa-miR-4796-5p 19 aagugacagaguauagaca 1 |
| 15 | MR274 | 67 | UserSeq 47 uguagaugaagaaggua 63<br>\|\|\|\|\|\| \|\|\|\|\|\|\| \|<br>hsa-miR-6867-5p 7 uguagaggaagaaggga 23 |

| S. No | Hairpin | Score | Alignment (SARS-CoV-2 and Human microRNA) |
|---|---|---|---|
| 16 | MR304 | 64 | UserSeq 68 ucugccuuguguggucugca 87<br>\|\|\|\| \|\| \|\|\|\|\| \|\|\|\|<br>hsa-miR-3064-5p 1 ucuggcuguuguggugugca 20 |
| | | 63 | UserSeq 19 aguagacuauauaucgua 36<br>\|\|\|\|\|\| \|\|\|\| \|\|\|\|<br>hsa-miR-411-5p 2 aguagaccguauagcgua 19 |

### 3.3. Hybridization between Viral Precursor miRNAs and Human miRNAs

RNAhybrid (https://bibiserv.cebitec.uni-bielefeld.de/rnahybrid?id=rnahybrid_view_submission), was utilized for the successful and positive hybridization of the human target miRNAs and miRNA precursors of SARS-CoV-2 measurement. Pairing energy revealed hybridization stability (or minimum free energy). A cut-off score was used to pick the potential miRNAs at -10 kcal/mol. In a large viral RNA hairpin, this software discovered the most energetically favorable miRNA hybridization sites. Effective hybridizations are shown in Table 2.

**Table 2.** MicroRNA and Viral RNA Hybridization using RNAhybrid Program

| S. No. | Target and miRNA | RNAhybrid Result | *mfe (kcal/mol) |
|---|---|---|---|
| 1 | MD3 & hsa-miR-4471 | Hit not found | |
| 2 | MD19 & hsa-miR-3675-3p | target 5' A U A G 3'<br>GUUUCU AG GAC<br>UAGAGA UC UUG<br>miRNA 3' G U C AG 5' | -13.7 |
| 3 | MD29 & hsa-miR-383-5p | Hit not found | |
| | MD29 & hsa-miR-5197-3p | target 5' A GCCA A 3'<br>GUUUGA UCA<br>UAAGCU AGU<br>miRNA 3' ACUG CAGAGAAGAA 5' | -11.6 |
| 4 | MD134 & hsa-miR-190b-5p | Hit not found | |
| 5 | MD 220 & hsa-miR-363-5p | target 5' UAUAA G 3'<br>CGUG CAC<br>GCAC GUG<br>miRNA 3' UUUAACGUA UAG GGC 5' | -12.7 |
| 6 | MD228 & hsa-miR-4802-3p | target 5' A UUUAC A 3'<br>GG AACC<br>CC UUGG<br>miRNA 3' UA UACCU AAGUU 5' | -11.0 |
| 7 | MD240 & hsa-miR-23b-5p | target 5' C A G 3'<br>UUGG AUGCU<br>AGUC UACGG<br>miRNA 3' UUU G UCCUU 5' | -12.3 |
| 8 | MD306 & hsa-miR-325 | target 5' G ACACCA G 3'<br>CUGG UCUAG<br>GAUC AGGUC<br>miRNA 3' G AUCCAC AUU 5' | -12.7 |

| S. No. | Target and miRNA | RNAhybrid Result | *mfe (kcal/mol) |
|---|---|---|---|
| | MD306 & hsa-miR-2114-5p | target 5' A G AGA A 3'<br>CC CUUCU AAGUG<br>GG GAAGG UUCGC<br>miRNA 3' A AAC CA 5' | -16.8 |
| 9 | MD307 & hsa-miR-215-3p | Hit not found | |
| | MD307 & hsa-miR-548y | Hit not found | |
| | MD307 & hsa-miR-338-3p | Hit not found | |
| | MD307 & hsa-miR-3065-5p | Hit not found | |
| 10 | MD311 & hsa-miR-4699-3p | Hit not found | |
| | MD311 & hsa-miR-6739-3p | Hit not found | |
| 11 | MR155 & hsa-miR-363-5p | target 5' A C UU C 3'<br>GUG AUC GAU<br>CAC UAG CUA<br>miRNA 3' C UG CGUUAAA 5' | -11.8 |
| 12 | MR165 & hsa-miR-153-5p | Hit not found | |
| 13 | MR186 & hsa-miR-744-3p | target 5' AAU UG C 3'<br>UUG UUAG UCAA<br>AAC GAUU AGUU<br>miRNA 3' AC GGU GG 5' | -10.3 |
| | MR186 & hsa-miR-4420 | target 5' C U G GU A 3'<br>AC GA GU GU<br>UG CU UA CA<br>miRNA 3' GUCGA U G GU C 5' | -13.1 |
| | MR186 & hsa-miR-448 | target 5' C G 3'<br>UGC UGUGUA<br>AUG AUACGU<br>miRNA 3' UGUAGG U 5 | -12.0 |
| 14 | MR243 & hsa-miR-4796-5p | Hit not found | |
| 15 | MR274 & hsa-miR-6867-5p | Hit not found | |
| 16 | MR304 & hsa-miR-3064-5p | target 5' G GU 3'<br>UGUG CUGCA<br>ACGU GGUGU<br>miRNA 3' GU UGUCGGUCU 5' | -11.7 |
| | MR304 & hsa-miR-411-5p | target 5' G UA C A 3'<br>AC UAUAU GU<br>UG AUAUG CA<br>miRNA 3' A CG C GAUGA 5' | -11.7 |

### 3.4. Secondary Structure miRNA Precursor

The pre-miRNA secondary structure was predicated using the online web-server tool RNAfold (http://rna.tbi.univie.ac.at/cgi-bin/RNAWebSuite/RNAfold.cgi) (Figures 4). The RNAfold results were used to predict SARS-CoV-2 hairpin sequences with the most stable secondary structures. Pre-miRNA, around 200bp from the precursor's end, was included in the sequence used for prediction analysis. Folding structures with a centroid were presented in every case.

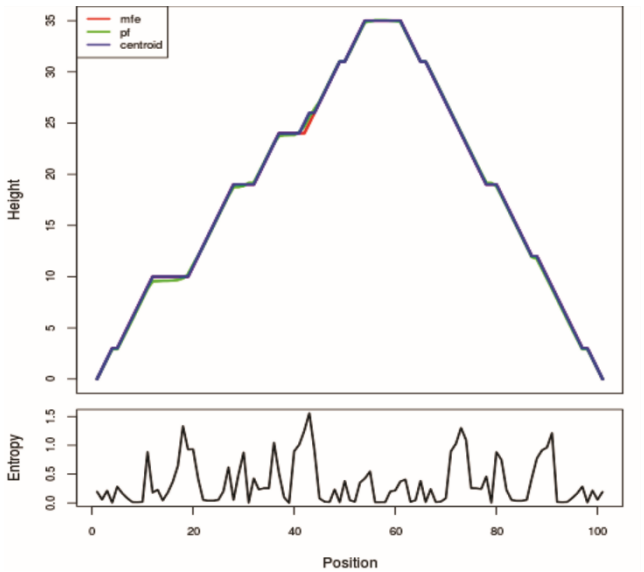


**Figure 3.** Predicated secondary structure of precursor miRNA hairpin – mounting plot

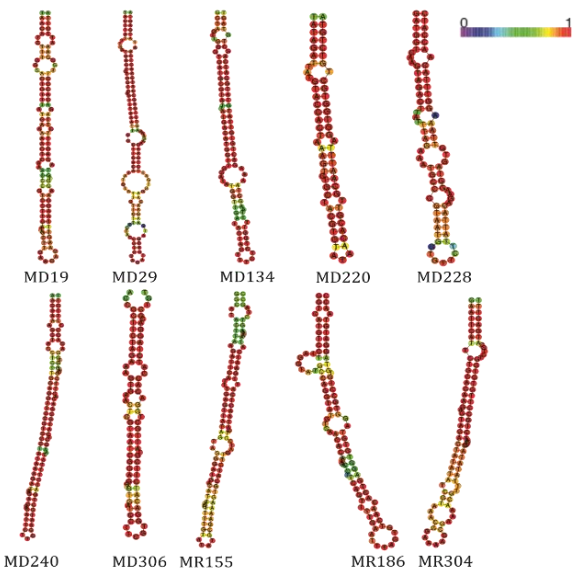


**Figure 4.** Structure *(Secondary)* of potential hairpin candidates of SARS-CoV-2

## 4. Discussion

Over the last few decades, miRNA research has been accelerated to explore the pathogenesis function and its role in the development of novel antiviral therapy [41]. MicroRNAs are ~ 21-nt non-coding RNAs derived from large primary miRNAs (pre-miRNAs) by binding to the 3' UTR of the target miRNAs, which slices gene expression post-transcriptionally and they are well conserved between different organisms [42, 43]. Each miRNA possesses hundreds of target genes and a single gene can be targeted by several miRNAs [44]. There is

increasing evidence suggesting that miRNAs use partial nucleotide sequence complementarity to suppress the expression of protein-coding genes and many biological processes, such as development, proliferation, differentiation (cellular), and pathophysiology are dependent on them [45].

Since the discovery of the first miRNAs, over 2,500 human and a total of 28,645 miRNA sequences have been stored in the miRbase [38, 46–48]. Since miRNAs are essential pos-transcriptional regulators of both viral and host gene expression, so they play a significant role in viral pathogenesis. In target selection, the ideal binding position between 3' UTR of the miRNA and the seed region (2 to 7 or 2 to 8 of the 5' ends of the miRNA) is essential, it should be sufficient for effective cleavage [48]. Due to a highly conserved nucleotide position upstream, the minimum pairing requirement is 5 – 6 nucleotide match [49, 50].

The SARS-CoV-2 genome was investigated using different bioinformatics methods, resulting in the identification of 16 potential miRNA precursors. Among those based on bioinformatics analysis were effective hybridization, hybridization pattern and pairing energy. We identified considerable sequence similarity with the SARS-CoV-2 genome where the seed region is concerned and it showed an ideal identity with 3' UTR of viral miRNA. So, we propose that hsa-miR-3675-3p (MD19), hsa-miR-325 (MD306), hsa-miR-2114-5p (MD306), hsa-miR-744-3p (MR186) and hsa-miR-448 (MR186) would be the best potential cellular target miRNAs to develop a post-exposure therapy.

## 5. Conclusion

In our current investigation, we identified miRNAs for SARS-CoV-2 in human beings using computational tools. This study was based on an interesting hypothesis of the utilization of host miRNA as a potential post-exposure therapy because the current evidence suggests that host miRNAs may down-regulate the viral gene expression.

Although most of the predicated human miRNAs of SARS-CoV-2 genome functions are yet to be discovered, still we hypothesize that those miRNAs may down-regulate viral gene expression to block its replication [51, 52]. However, further *in vitro* research is needed to determine the effect of chosen miRNAs on viral replication inhibition.

## Conflict of Interest

The authors declare no conflict of interest.

## Funding

None

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