Review Article

Predicting MicroRNAs as Anti-Viral Agents in SARS-CoV-2 Infection based on the Bioinformatics Approach: A Systematic Review

Mona Fani[1,2], Hasan Namdar-Ahmadabad[1,2], Amir Azimian[1], Hamed Ghasemzadeh-moghaddam[1,2*]

Abstract

At the beginning of 2020, the World health organization (WHO) declared severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) as responsible for the coronavirus disease 2019 (COVID-19) outbreak. Previous studies showed that microRNAs (miRNAs) can inhibit the pathogenesis of DNA or RNA viruses by binding the genome. The purpose of the current study was an overview of the anti-viral role of cellular miRNAs against COVID-19 infection. Our search was limited to all published original papers in the English language from 2019 to 2021 using several databases including PubMed, Google Scholar, Scopus, and Science Direct. A manual search of references for included articles was also performed. Among 66 electronically searched citations, 17 papers met the inclusion criteria. The presence of miRNAs during the COVID-19 infection, reported by several studies, predicts the possibility of using miRNAs as potential tools to eradicate the SARS-CoV-2 infection. In some studies, miRNAs have presented as a tool for targeting SARS-CoV-2 encoded genes which are essential in viral biogenesis, entrance, replication, and infection. The comparison of miRNA between SARS-CoV-2 with other human coronaviruses will help the better understanding of distinct clinical characteristics.

1. Department of Pathobiology and Laboratory Sciences, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran
2. Vector-borne Diseases Research Center, North Khorasan University of Medical Sciences, Bojnurd, Iran

***Corresponding Author:**
Hamed Ghasemzadeh-Moghaddam, Department of Pathobiology and Laboratory Sciences, School of Medicine, North Khorasan University of Medical Sciences, Bojnurd, Iran.
Email: h_gh497@yahoo.com

Keywords: SARS-CoV-2, COVID-19, miRNA, microRNA, anti-viral

Please cite this article as: Fani M, Namdar-Ahmadabad H, Azimian A, Ghasemzadeh-Moghaddam H. Predicting MicroRNAs as Anti-Viral Agents in SARS-CoV-2 Infection based on the Bioinformatics Approach: A Systematic Review. J Cell Mol Anesth. 2021;6(2):141-7. DOI: https://doi.org/10.22037/jcma.v6i2.33737

Introduction

Highly pathogenic zoonotic coronaviruses have been reported over the past two decades, including severe acute respiratory syndrome-Coronavirus (SARS-CoV), and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2002/2003 and 2012. Recently, the outbreak of Coronavirus Disease 2019 (COVID-19) was caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and distributed worldwide (1). Patients with underlying diseases like Acute Respiratory Distress Syndrome (ARDS), Diabetes mellitus, cardiovascular diseases, hepatitis, enteric diseases, and central nervous diseases have a greater risk of mortality when infected with COVID-19 (2).

SARS-CoV-2 belongs to β CoV and is a positive-single-stranded RNA (+ssRNA) virus with a

genome size of 30kb. In addition to non-structural proteins, SARS-CoV-2 encodes structural proteins like the spike protein (S), an envelope protein (E), membrane protein (M), the nucleocapsid protein (N) as well (3).

SARS-CoV-2 is more contagious than SARS-CoV (4) while sequence base analysis illustrates almost 79% similarity among them. Two unforeseen O-glycosylation sites on the receptor-binding domain (RBD) of the virus probably increase the pathogenicity of COVID-19 during infection (5). The S1 subunit of S protein that contains RBD binds to the angiotensin-converting enzyme 2 (ACE2) on alveolar epithelial cells, using TMPRSS2 as a cellular protease for priming of SARS-COV-2 S glycoprotein when the S2 subunit facilitates the fusion and entrance process. Actually, ACE2 and TMPRSS2 have the critical roles during host cell entry phase of virus (5, 6).

The main strategies for preventing the SARS-CoV-2 infection are inhibiting the viral replication viral proteins synthesis and obstruction of virus entry (7). On the other hand, experimental pieces of evidence showed that some host-encoded MicroRNAs (miRNAs) can facilitate an intracellular defense tool against some RNA viruses (8). Therefore, miRNAs can repress the viral transcription or translation via binding to the 3′ untranslated region (3′UTR) of the viral messenger RNA (mRNA). In fact, after the formation of an RNA-induced silencing complex (RISC), miRNA can bind to 3′-UTR and the coding region of a target gene to induce translation repression or mRNA degradation. MiRNAs are non-coding and short RNAs that negatively regulate gene expression and involve in various pathologies such as cancer, apoptosis, and metabolism (8).

The levels of many pro-inflammatory effector cytokines, such as TNF, IL-1β, IL-6, IL-8, G-CSF, and GM-CSF, as well as chemokines, such as MCP1, IP10, and MIP1α, are elevated in SARS-CoV-2 infection. On the other hand, miRNAs can decrease the levels of these immunomodulatory factors as a molecular brake to modulate inflammation (3). Hence, the development of a miRNAs-based vaccine is highly useful to inhibit COVID-19 infection.

Researchers struggle to develop an effective SARS-CoV-2 vaccine to control and eradicate SARS-CoV-2 infections. Therefore, understanding the behavior of miRNAs may create new opportunities for the development of the miRNA-based anti-viral for SARS-CoV-2 infection. This systematic review attempts to help interested researchers for choosing the potent strategy to control COVID-19 by collecting the data on bioinformatic identification of miRNA-based interactions between the cellular miRNAs and viral or human genes.

Methods

Literature search: This systematic research was conducted for the over the research studies published on bioinformatics identification of microRNA mediated interactions in COVID-19 infection from 2019 to September 2020 using several national and international databases including; Pubmed, Google Scholar, Scopus, and Science Direct (fig. 1). The research was limited to the original articles published in English. The following keywords were used from medical subject headings: titles or abstracts “Severe Acute Respiratory Syndrome- Coronaviruses-2” OR “SARS-COV-2” OR “2019 Novel Coronavirus” OR “Novel Coronaviruses” AND “miRNA” OR “microRNA” OR “Non-Coding RNA”. The search was performed by 2 independent researchers.

Study selection: All the articles including the full text, abstract, pieces of evidence, and reports were provided for the current systematic review. We first exclude all duplicates. Then, irrelevant papers were deleted after reviewing titles, abstracts, and full texts. Generally, we reviewed articles that introduced miRNAs that were attached to structural and non-structural proteins. Finally, 17 papers were used for our study (Fig. 1).

Data extraction: The data were extracted from 17 selected articles, including the first author, country, year of publication, Human miRNA, viral target gene, and cellular target gene were extracted (Fig. 1).

Results

In the current review study, 66 articles were identified through the initial searches, among them, 17 articles met the inclusion criteria and 14 articles were excluded

because of being review articles, letters to editors, or having irrelevant titles. Table 1 presents a summary of the involved cellular miRNAs

Table 1: Vasoactive inotrope score in various groups.

Ref	Study by	Human miRNA	Viral target gene	Cellular target gene
[9]	Khan (Bangladesh, 2020)	miR-17-5p miR-20b-5p miR-323a-5p	ORF1ab, S, M, N region ORF3a ORF7a 3'UTR, 5'UTR	-
[10]	Ivashchenko, (Kazakhstan, 2020)	miR-4778-3p miR-6864-5p miR-5197-3p	3'UTR, 5'UTR	-
[11]	Liu (China, 2020)	miR-4661-3p	S region	-
[12]	Fulzele (USA, 2020)	miR-15b-5p, miR-15a-5p miR-548c-5p, miR-548d-3p miR-409-3p, miR-30b-5p, miR-505-3p	3'UTR coding region	-
[13]	Nersisyan (Russia, 2020)	let-7e, mir-125a, mir-141, miR-200	-	ACE2 / TMPRSS2
[14]	Lu (Germany, 2020)	miR-200c-3p	-	Ace2 mRNA and Ace2 protein
[15]	Haddad (Amman, 2020)	hsa-miR-3620-3p	S region	-
[16]	Teodori (Italy, 2020)	miR-335-5p, miR-26b-5p	S region	ACE2
[17]	Nersisyan (Russia, 2020)	miR-21-3p, miR-16- 5p/195-5p/424- 5p, miR-3065-5p and miR- 421	-	These miRNAs can regulate all human coronaviruses via direct binding to viral RNAs.
[7]	Balmeh (Iran, 2020)	miR-1307-3p	3′UTR	1.TGF- and semaphorin signaling 2.PI3K/Act signaling pathway 3.endocytosis signaling pathway 4.type 2 diabetes signaling pathway
[18]	Rakhmetullina (Kazakhstan, 2020)	miR-1273a, miR-1273d, miR-1272, miR-1292-5p, miR-3143, miR-1226-5p, miR-7161-3p	ORF1ab S and N region	-

[19]	Arisan (the UK, 2020)	miR-8066	N region	1.Activation of NfKB-mediated TLR-8 expression 2.Activation of the cytokine storm 3. Alteration of N-glycosylation patterns
		miR-3934-3p	-	1.glycosaminoglycan biosynthesis heparan sulfate (Heparan sulfate proteoglycans can provide the binding sites for SARS-CoV-2) 2.Vitamin digestion and absorption (vitamin D and B3 deficiency are associated with SARS-CoV-2 infection)
[20]	Demirci (Turkey, 2020)	miR-447b, miR-2052, miR-3127-5p, miR-34b-5p, miR-374a-3p	S region	-
		miR-3672	E region	-
		miR-325, miR-34a-5p, miR-6820-5p, miR-1252-5p, miR-1262	M region	-
		miR-8066, miR-1911-3p, miR-4259, miR-6838-3p, miR-208a-5p	N region	-
		miR-153-5p, let-7c-5p, miR-1910-3p, miR-342-5p, miR-4436b-3p	ORF1ab	-
		miR-549a-3p, miR-1246, miR-7704, miR-203b-3p, miR-342-5p	ORF3a	-
		miR-12129, miR-5047, miR-148a-3p, miR-23b-5p, miR-5011-3p	ORF8	-
		miR-4436a, miR-3135b, miR-4436b-3p, miR-4774-5p, miR-6731-5p	ORF7a	-
		miR-3682-5p, miR-411-5p, miR-379-5p, miR-548v	ORF10	-
		miR-190a-5p	ORF6	-

		miR-6762-3p, miR-6746-5p, miR-636, miR-6842-3p, miR-449a	3′UTR	-
[21]	Demongeot (France, 2020)	miR-129-5p	S region ORF10	-
[22]	Chow (Canada, 2020)	miR-5047	M	-
		miR-1301-3p	N	-
		miR-153-5p	ORF1ab	-
[23]	Baldassarre (Italy, 2020)	miR-4507, miR-638, miR-3150b-3p and miR-602	5′UTR	-
[24]	Sardar (India,2020)	mir-27b-3p	-	ACE2

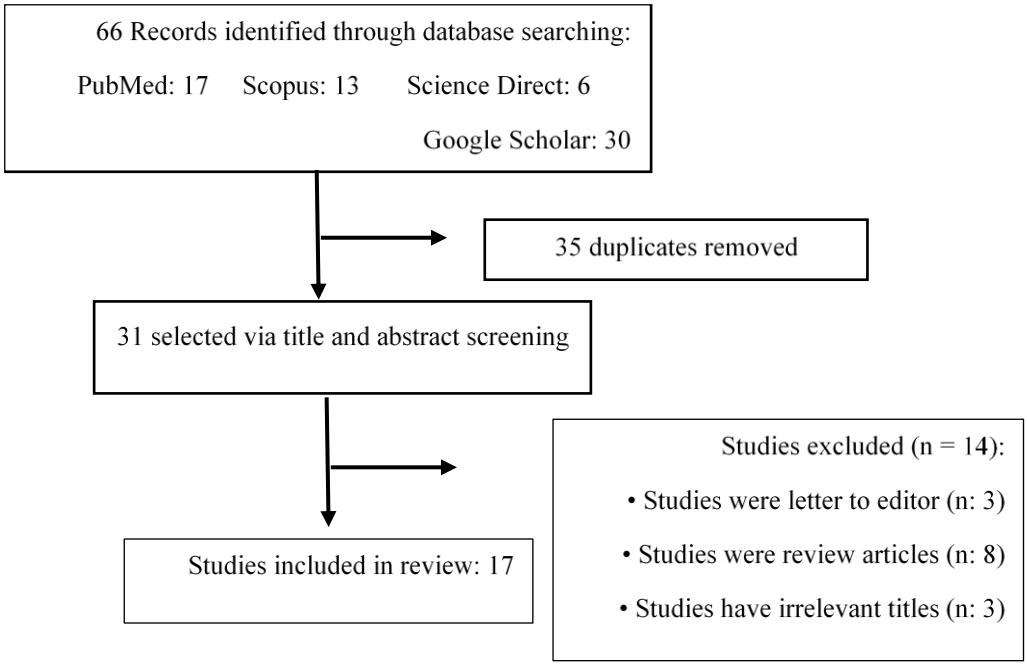

Figure 1. Flowchart of the search strategy.

in COVID-19 infection in the 17 articles reviewed.

Discussion

The pandemic of SARS-CoV-2 is a serious public health crisis that raised plenty of global concerns. Access to appropriate therapeutics can confine the COVID-19 disease in human communities.

The presence of miRNAs during the COVID-19 infection, reported by several studies (table 1), predicts the possibility of using viral or cellular miRNAs as potential tools to eradicate the SARS-CoV-2 infection. Indeed, in some studies, miRNAs have presented as a tool for targeting SARS-CoV-2 encoded genes which are essential in viral biogenesis, entrance, replication, and infection (Table 1).

Khan et al. reported that SARS-CoV-2 can encode miRNAs that can target the broad immune signaling pathways such as the insulin signaling pathway and complicate the condition of COVID-19 patients with underlying diabetic problems. Also, some SARS-CoV-2 miRNAs can target autophagy and IFN-I signaling that resulted to prolong the latent phase without any symptoms of COVID-19 and also increasing anomalies in underlying patients. In another study, Liu et al. reported that SARS-CoV-2 produces a miRNA (MR147-3p) which increases the infection due to the overexpression of TMPRSS2 that cleaves the S glycoprotein. Furthermore, some cellular miRNAs can regulate the ACE2 and TMPRSS2 expression that have an enzymatic role and are essential for cell entrance of virus during COVID-19 infection.

Moreover, some cellular miRNAs such as miR-8066 act as a double-edged sword in COVID-19 disease. MiR-8066 can target the RBD of subunit S1 to block the attachment of SARS-CoV-2 to ACE2, and also it is associated with the cytokine storm in SARS-CoV-2 infection. On the other hand, several studies have shown that miRNA expression decreases in aged patients with underlying conditions resulted in better replication of the SARS-CoV-2 genome and more viral particle production in comparison to younger people. In fact, in young individuals, miRNAs bind to viral genomes more successfully and prevent the accumulation of viral particles (9).

There is an antiviral role for cellular miRNAs when some viruses can manipulate and degrade cellular miRNAs to inhibit their maturation for their advantage (8). Therefore, investigation on the potential roles of miRNA in host-virus interaction is essential to design an appropriate vaccine for COVID-19.

Moreover, some of the blood-based biomarkers such as miR-146a-5p that have been found in the patients infected by COVID-19 can suggest a molecular link between SARS-CoV-2 infection and inflammation, therefore these findings open a new window in understanding SARS-CoV-2 pathogenesis to cure COVID-19 infection.

In reviewed articles here, a lot of miRNAs are introduced, their interactions with the SARS-CoV-2 genome should be examined via further in-vivo and in-vitro studies to validate the potential therapeutic targets. Studies on the side effects of these miRNAs in humans are needed when further research is required on plenty of patient-derived samples. Furthermore, the comparison of miRNA between SARS-CoV-2 with other human coronaviruses will help the better understanding of distinct clinical characteristics.

Conclusion

The comparison of miRNA between SARS-CoV-2 with other human coronaviruses will improve our knowledge about its distinct clinical characteristics.

Acknowledgment

This research was supported by Shahid Beheshti University of Medical Sciences, Tehran, Iran [Project no. 25349].

Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

1. Hui DS. Epidemic and Emerging Coronaviruses (Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome). Clin Chest Med. 2017;38(1):71-86.
2. Rizzo P, Vieceli Dalla Sega F, Fortini F, Marracino L, Rapezzi C, Ferrari R. COVID-19 in the heart and the lungs: could we "Notch" the inflammatory storm? Basic Res Cardiol. 2020;115(3):31.
3. Fani M, Teimoori A, Ghafari S. Comparison of the COVID-2019 (SARS-CoV-2) pathogenesis with SARS-CoV and MERS-CoV infections. Future Virol. 2020:10.2217/fvl-020-0050.
4. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020;367(6483):1260-3.
5. Widiasta A, Sribudiani Y, Nugrahapraja H, Hilmanto D, Sekarwana N, Rachmadi D. Potential role of ACE2-related microRNAs in COVID-19-associated nephropathy. Noncoding RNA Res. 2020;5(4):153-66.
6. Glowacka I, Bertram S, Müller MA, Allen P, Soilleux E, Pfefferle S, et al. Evidence that TMPRSS2 activates the severe acute respiratory syndrome coronavirus spike protein for membrane fusion and reduces viral control by the humoral immune response. J Virol.

2011;85(9):4122-34.
7. Balmeh N, Mahmoudi S, Mohammadi N, Karabedianhajiabadi A. Predicted therapeutic targets for COVID-19 disease by inhibiting SARS-CoV-2 and its related receptors. Inform Med Unlocked. 2020;20:100407.
8. Fani M, Zandi M, Rezayi M, Khodadad N, Langari H, Amiri I. The Role of microRNAs in the Viral Infections. Curr Pharm Des. 2018;24(39):4659-67.
9. Fulzele S, Sahay B, Yusufu I, Lee TJ, Sharma A, Kolhe R, et al. COVID-19 Virulence in Aged Patients Might Be Impacted by the Host Cellular MicroRNAs Abundance/Profile. Aging Dis. 2020;11(3):509-22.
10. Khan MA, Sany MRU, Islam MS, Islam A. Epigenetic Regulator miRNA Pattern Differences Among SARS-CoV, SARS-CoV-2, and SARS-CoV-2 World-Wide Isolates Delineated the Mystery Behind the Epic Pathogenicity and Distinct Clinical Characteristics of Pandemic COVID-19. Front Genet. 2020;11:765.
11. Canatan D, De Sanctis V. The impact of MicroRNAs (miRNAs) on the genotype of coronaviruses. Acta Biomed. 2020;91(2):195-8.
12. Farshbaf A, Mohtasham N, Zare R, Mohajertehran F, Rezaee SA. Potential therapeutic approaches of microRNAs for COVID-19: Challenges and opportunities. J Oral Biol Craniofac Res. 2021;11(2):132-7.
13. Nersisyan S, Shkurnikov M, Turchinovich A, Knyazev E, Tonevitsky A. Integrative analysis of miRNA and mRNA sequencing data reveals potential regulatory mechanisms of ACE2 and TMPRSS2. PLoS One. 2020;15(7):e0235987.
14. Lu D, Chatterjee S, Xiao K, Riedel I, Wang Y, Foo R, et al. MicroRNAs targeting the SARS-CoV-2 entry receptor ACE2 in cardiomyocytes. J Mol Cell Cardiol. 2020;148:46-9.
15. Haddad H, Walid A-Z. miRNA target prediction might explain the reduced transmission of SARS-CoV-2 in Jordan, Middle East. Noncoding RNA Res. 2020;5(3):135-43.
16. Teodori L, Sestili P, Madiai V, Coppari S, Fraternale D, Rocchi MBL, et al. MicroRNAs Bioinformatics Analyses Identifying HDAC Pathway as a Putative Target for Existing Anti-COVID-19 Therapeutics. Front Pharmacol. 2020;11:582003.
17. Nersisyan S, Engibaryan N, Gorbonos A, Kirdey K, Makhonin A, Tonevitsky A. Potential role of cellular miRNAs in coronavirus-host interplay. PeerJ. 2020;8:e9994.
18. Demongeot J, Seligmann H. SARS-CoV-2 and miRNA-like inhibition power. Med Hypotheses. 2020;144:110245.
19. Arisan ED, Dart A, Grant GH, Arisan S, Cuhadaroglu S, Lange S, et al. The Prediction of miRNAs in SARS-CoV-2 Genomes: hsa-miR Databases Identify 7 Key miRs Linked to Host Responses and Virus Pathogenicity-Related KEGG Pathways Significant for Comorbidities. Viruses. 2020;12(6).
20. Saçar Demirci MD, Adan A. Computational analysis of microRNA-mediated interactions in SARS-CoV-2 infection. PeerJ. 2020;8:e9369.
21. Marchi R, Sugita B, Centa A, Fonseca AS, Bortoletto S, Fiorentin K, et al. The role of microRNAs in modulating SARS-CoV-2 infection in human cells: a systematic review. Infection, genetics and evolution : journal of molecular epidemiology and evolutionary genetics in infectious diseases. 2021;91:104832.
22. Chow JT, Salmena L. Prediction and Analysis of SARS-CoV-2-Targeting MicroRNA in Human Lung Epithelium. Genes (Basel). 2020;11(9).
23. Baldassarre A, Paolini A, Bruno SP, Felli C, Tozzi AE, Masotti A. Potential use of noncoding RNAs and innovative therapeutic strategies to target the 5'UTR of SARS-CoV-2. Epigenomics. 2020;12(15):1349-61.
24. Khan MI, Khan ZA, Baig MH, Ahmad I, Farouk AE, Song YG, et al. Comparative genome analysis of novel coronavirus (SARS-CoV-2) from different geographical locations and the effect of mutations on major target proteins: An in silico insight. PLoS One. 2020;15(9):e0238344.