Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review

MicroRNAs in the development of potential therapeutic targets against COVID-19: A narrative review

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ABSTRACT

Background: As the therapeutic regimens against the COVID-19 remain scarce, the microRNAs (miRNAs) can be exploited to generate efficient therapeutic targets. The miRNAs have been found to play pivotal roles in the several regulatory functions influencing the prognosis of viral infection. The miRNAs have a prospective role in the up and down regulation of the ACE2 receptors. This review examines the clinical applications, as well as the possible threats associated with the use of miRNAs to combat the deleterious consequences of SARS-CoV-2 infection.
Methodology: This article was compiled to evaluate how the miRNAs are involved in the SARS-CoV-2 pathogenesis and infection, and their potential functions which could help in the development of therapeutic targets against the COVID-19. The sources of the collected information include the several journals, databases and scientific search engines such as the Google scholar, Pubmed, Science direct, official website of WHO, among the other sites. The investigations on the online platform were conducted using the keywords miRNA biogenesis, miRNA and ACE2 interaction, therapeutic role of miRNAs against SARS-CoV-2 and miRNA therapy side effects.
Results: This review has highlighted that the miRNAs can be exploited to generate potential therapeutic targets against the COVID-19. Changes in the miRNA levels following viral replication are an essential component of the host response to infection. The collection and modification of miRNA modulates may help to minimize the deleterious consequences of SARS-CoV-2 infection, such as by controlling or inhibiting the generation of cytokines and chemokines. The degradation of viral RNA by the cellular miRNAs, along with the reduced expression of ACE2 receptors, can substantially reduce the viral load. Specific miRNAs have been found to have an antiviral influence, allowing the immune system to combat the infection or forcing the virus into a latency stage.
Conclusion: This review summarizes several studies revealing the involvement of miRNAs in diverse and complex processes during the infection process of SARS-CoV-2. The miRNAs can substantially reduce the viral load by degradation of viral RNA and reduced expression of ACE2 receptors, besides mitigating the deleterious consequences of the exaggerated secretion of cytokines. Extensive investigations need to be done by the scientific community to utilize the miRNA based strategies for the development of effective therapeutic targets against the COVID-19.

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Contents

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes the new coronavirus disease 2019 (COVID-19), which belongs to the group of *beta coronaviruses* in the Coronaviridae family [1], which has the closest relationship and likelihood with the previously emerged SARS-CoV in 2003 that was known by SARS outbreak [2,3]. Human coronaviruses (HCoVs) infections usually target upper and lower respiratory tract infections. Some of the human coronaviruses like a human coronavirus NL63 (HCoV-NL63), human coronavirus OC43 (HCoV-OC43), and human coronavirus HKU1 (HCoV-HKU1), comes as minor infection and lead to common colds [2]. Moreover, during the last two decades, a group of highly infectious coronaviruses with a severe infection in the human population have been characterized, comprising severe acute respiratory syndrome coronavirus (SARS-CoV), that resulted in an outbreak in the year 2003 and infected more than 8000 people globally with a mortality rate of around 10 %. Middle East respiratory syndrome coronavirus (MERS-CoV) appeared in the year 2012 and infected around 2500 people with a fatality rate of around 37 % [4]. Several studies have revealed that such a highly pathogenic coronavirus resulted in severe and acute respiratory distress syndrome (ARDS), resulting in diffused inflammation in the respiratory system, difficulty in breathing, and even death. In contrast, SARS-CoV-2 has a tendency to spread more rapidly than SARS-CoV-1 and MERS; however, the fatality rate tends to be lower than 2–3 % in comparison [5,6].

The COVID-19 pandemic has resulted in 516 million cases with a fatality of 6.2 million people worldwide, as well as posing significant problems to healthcare facilities and medical infrastructure [7,8]. This situation has sparked widespread alarm, as well as threats and financial losses all around the world [7]. Furthermore, because COVID-19 is a unique virus, the US Food and Drug Administration (FDA) has not approved any specific treatments for it, necessitating an urgent search for effective and safe therapeutic agents [8–10]. The immune response is vital for controlling and resolving SARS-CoV-2 infections, but it can also cause cellular damage, which is linked to an aggravated immunological response [11,12]. MicroRNAs (miRNAs) were discovered to play a key part in the intricate network of interactions between the etiological agent and infected host cells [11–13]. A cytokine storm-generated during viral infection, particularly in the case of SARS-CoV-2, has been found to result in an overactive immunological response that is significantly harmful to host cells [12–14]. Recent data has suggested that the collection of miRNAs modulates each of these stages, and these miRNAs can be exploited to generate therapeutic targets for the reliable and efficient treatment of patients with COVID-19 [15]. As a result, manipulating miRNAs may help to minimize COVID-19's pathogenic effects and reduce the deleterious consequences of SARS-CoV-2 infection [9], such as by controlling or inhibiting the generation of cytokines and the chemokines. Among several nucleic acid-based therapeutic approaches, miRNAs have been postulated as one of the promising therapeutic strategies to combat COVID-19 [15,16].

MicroRNAs (miRNA) are non-coding RNAs, small molecules with nucleotides length of around 17–25 [17]. miRNAs at most are produced by transcription from DNA template to produce primary miRNAs and subsequently go under process to produce precursor miRNAs, and mature miRNAs produce precursor miRNAs and mature miRNAs. Mainly, miRNAs anneal to the 3′ UTR of target messenger RNAs (mRNA) [18] and are significant regulators of the gene expression process at the post-transcriptional level. miRNAs play a decisive function in different biological phenomena, including cell propagation, differentiation, growth, and apoptosis [19]. Nevertheless, it has been revealed that miRNAs anneal to additional positions on the mRNA, comprising the 5′ UTR, gene promoters, and coding sequence [20]. Additionally, miRNAs have been reported to trigger gene expression in some circumstances [21]. Recently researchers have proposed that miRNAs play a crucial role in controlling the transcription and translation rate through moving between various subcellular compartments [22]. Lee and his colleagues in 1993, discovered miRNAs for the first time. They have found that they have a role in the down-regulation of an essential protein called LIN-14, responsible for developing the *Caenorhabditis elegans* nematode larvae from the L1 stage to the L2 stage [23]. The miRNA biogenesis is an active process that consists of many steps that lastly lead to the production of mature miRNAs [24]. Due to the complexity of the miRNA's transcription, maturation, and functioning, any disruption in these processes can interrupt the miRNA synthesis pathway and biological activities, which may severely decrease or increase miRNA production in a particular tissue. The perturbations in the miRNA's synthetic pathway and their biological activities can lead to a poor prognosis of the diseases, especially in the case of SARS-CoV-2 infection [25,26].

Numerous studies have found that miRNAs play a significant role in the interaction of viruses and host cells. Despite the fact that the role of host miRNAs in SARS-CoV-2 infection has been predicted, experimental data are still lacking [26]. Furthermore, clinical trials have yet to demonstrate that antiviral miRNAs can be used to modulate the host immune response to SARS-CoV-2 infection. The genomic difference that, as a result, controls the host miRNA target sites and viral miRNAs might explain the difference between SARS-CoV and various isolated SARS-CoV-2 in terms of pathogenesis and infectivity [27]. Therefore, seeking new biological strategies for treating viral diseases is highly recommended. It is essential to

notice that the previous along with recent shreds of the data imply that miRNAs can play important functions in modulating the immune system toward respiratory viruses, such as Human coronaviruses (HCoVs) that includes SARS-CoV-1, MERS, SARS-CoV-2, and other types of HCoVs, human metapneumovirus (hMPV), human rhinovirus (hRV), IV, and RSV. Also, changes in the expression of miRNAs in epithelial cells may participate in the pathogenesis of both severe and chronic respiratory infections [9,28]. Although underappreciated, miRNAs expressed in human lung cells may also be an important factor in determining COVID-19's severity [29]. Hence, modulation of miRNAs might mitigate COVID-19 pathological negative effects and decrease host damage.

In addition, the role of miRNAs in the infectivity of coronaviruses has not been examined in-vivo studies [30]. Furthermore, it has been demonstrated that high-dose single miRNA administration is required to obtain the best therapeutic efficiency and reliability, but the administration of the high dose of single-miRNA can have negative consequences. As a result, a cocktail of miRNAs may have fewer off-target effects and be more effective than monotherapy [31,32]. The production of miRNAs and their significance in the control of the host immune response are the subjects of this review. The clinical application of miRNAs, as well as the possible threats connected with their use, is also highlighted in this review.

Genomic architecture of SARS-CoV-2

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA [33], and its genetic material is the largest of all RNA viruses [34]. SARS-CoV-2 genome size is around 30 kb and is translated into a total of 29 proteins of functional and viral structural proteins. Over two-thirds of the genome of SARS-CoV-2 is composed of orf1ab at the 5' end of the sequence, which encodes orf1ab polyproteins. In contrast, the rest of the genome contains the structural protein encoded genes which are spike protein (S), an envelope protein (E), membrane protein (M), and nucleocapsid protein (N) at the downstream of the viral RNA genome. Furthermore, the genome of SARS-CoV-2 has six more genes that include "ORF3a, ORF6, ORF7a, ORF7b, and ORF8 genes" that code for six additional proteins [35,36]. The structural and genomic organization of SARS-CoV-2 has been demonstrated in Fig. 1.

Biogenesis of miRNAs

MicroRNAs (miRNAs) are highly conserved, small (about 22 bp long), non-coding single-stranded ribonucleic acids (RNAs) that control the expression of complementary messenger RNAs (mRNAs). They repress the translation of target mRNA by binding to the 3' ends in the untranslated regions (UTRs) or to a specific region in open reading frames (ORFs) of mRNA transcription [34]. In humans and other eukaryotic species, miRNA biogenesis occurs in two stages, with nuclear and cytoplasmic cleavage events [38,39].

Transcription of miRNA in the nucleus

The biogenesis mechanism of miRNA starts in the nucleus through the transcription from genes encoding for miRNA through RNA polymerase II, or RNA polymerase III, leading to the formation of a primary transcript that encodes miRNA called pri-miRNAs of a hairpin structure of about 1000 nucleotides (nt) long [37]. This stage is negatively or positively controlled through RNA polymerase II-associated transcription factors, including ZEB1, ZEB2, MYC, and p53, as well as epigenetic modulators like the DNA methylation and modification of histones [40]. RNA pol II is considered to be accountable for most of miRNA's transcription between two RNA pol enzymes, RNA pol II and RNA pol III (Fig. 2). The size of pri-miRNA, which is usually more than 1 kb lengthy than the pol III transcripts, demonstrates the priority for RNA pol II. In addition, pri- miRNA contains uridine residue sequences that stop pol III transcriptions [39]. These snippets of information bolster the idea that RNA pol II is involved in the transcription of most of the pri-miRNAs. Nevertheless, it is important to note that RNA pol III is involved in the transcription of certain miRNAs, such as miR-142 [41]. In addition to the aforementioned characteristics, transcriptional start locations are positioned far from the genes, and promoters comprise RNA pol II-specific features [39–42]. The transcriptional control of miRNAs can sometimes be described as a feedback loop in which positive or negative regulations of miRNA can decrease or amplify their own transcription [39–43]. Around half of the recognized miRNAs are intragenic and commonly transcribed from introns (non-protein coding genes). In contrast, transcription from exons (protein-coding genes) is moderately limited. These transcription processes are independent of their host genes and are controlled through their own specific promoters [44]. Sometimes, miRNAs transcription comes as a single extended sequence known as miRNAs clusters. This can have a related target position; hence they are considered as family miRNAs [45].

Genesis of pre-miRNA in the nucleus

Following the miRNA transcription genes through RNA polymerase II in the nucleus, the primary miRNA undergoes several maturation cycles. The first-ever step of primary miRNA processing occurs in the nucleus, and the Ribonuclease III (RNase III) Drosha, alongside the help of DGCR8 (DiGeorge syndrome critical region gene 8) co-factor, produces the Microprocessor complex that cleaves the primary miRNA loop end, resulting in the formation of precursor miRNA, named pre-miRNAs that has a hairpin structure of about 70 nucleotides (nt) long [46] (Fig. 2). Furthermore, pri-miRNA transforms into an operational miRNA with a flexible terminal loop of approximately ten bp and 5′ phosphate, as well as two nt (nucleotide) 3′ ssRNA (single-stranded RNA) overhangs. Drosha, an RNase III endonuclease, and the dsRNA (double-stranded RNA)-binding protein DGCR8, also known as pasha, are involved [38–47]. The pre-miRNA features a staggered cut with a 5′ phosphate and 3′ overhang of 2 nt [47].

Maturation of pri-miRNAs into the mature miRNAs in the cytoplasm

The produced precursor miRNAs are transported into the cytoplasm through Exportin-5 to go through the subsequent stages of maturation [48]. Here, precursor miRNAs are cleaved again by an enzyme called Dicer, a cytoplasmic RNase endonuclease, to form mature duplex miRNAs of around 22 nt long [49,50]. Furthermore, the produced miRNAs duplex, along with the protein named argonaute (AGO), further produces the miRNA-induced silencing complex (miRISC) [50]. The miRNA biosynthesis reveals the processes that control the expression of its target gene shown in Fig. 2 (Fig. 2). Regulation of genes and intercellular signaling is the main significant function played by miRNAs [18]. In terms of gene regulations, the formed miRISC can function through two pathways called canonical and non-canonical pathways [51]. In the canonical pathway, miRISC anneals to the 3' UTR of the targeted mRNA, resulting in the translation termination process when both strands are exactly complementary to each other, or leading to a reduction in both strands are exactly complementary to each other or reducing translation during limited complementarity between two strands [52]. In contrast, complete complementarity is not required by the non-canonical pathway [53]. One miRNA may regulate many mRNAs, but also, one mRNA may be regulated by several miRNAs [54].

Recent studies have shown miRNAs play pivotal roles in several regulatory functions which decide the prognosis of the infection, especially in viral infections. Generally, its known that viruses are

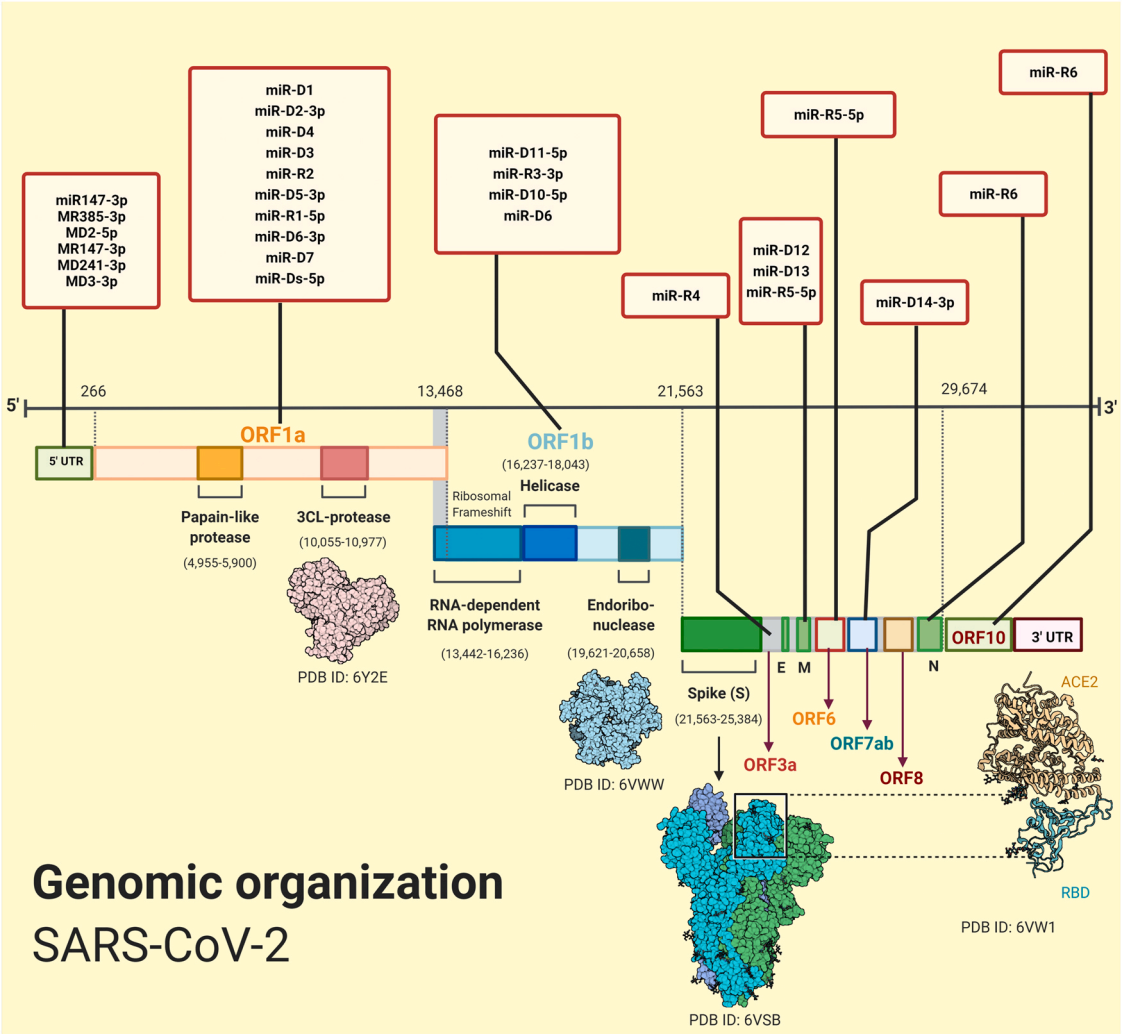

Fig. 1. Structural organization of SARS-CoV-2 genome and viral induced miRNA.

obligate intracellular pathogens whereby only count on the targeted cell for replication and infection [13]. Viruses are known to have the capability to upregulate or downregulate key miRNAs of the host to gain the ability to evade the host's immune response [55]. Conversely, specific miRNAs were discovered to have an antiviral influence, allowing the immune system to combat the infection or forcing the virus into a latency status [56]. Keeping all the above points in mind, we summarise how miRNAs are involved in SARS-CoV-2 pathogenesis and infection processes, and the potential functions they provide might help find and develop an antiviral therapeutic agent for many viral infections that do not have a complete cure in the meantime.

Therapeutic potential of miRNAs against SARS-CoV-2

Viruses replicate their genetic material by using the host's cellular machinery. During this process, interactions can occur between host miRNAs and the viral genome. These interactions can occur via three pathways: mRNA blocking, mRNA destabilization, and mRNA degradation via protein complexes [57]. In addition to the host miRNAs, some viruses can generate their miRNAs [58]. The miRNAs of the virus take part in the replication cycle in the infected host cell and might result in some alterations in the infected cell [59] (Fig. 3). Concerning the role, the host miRNAs are categorized as proviral or antiviral depending on the actions during a certain viral infection. The interaction between the host and viral miRNAs might allow the virus to replicate in the host cell and extend the infection to other cells, consequently bringing about proviral roles [60]. Additionally, proviral miRNAs can allow a viral infection through antiviral factors suppression like interferons (IFNs), letting the virus do an immune evasion of the host immune system [61].

There are different ways against the SARS-CoV-2 infection: inhibiting the viral replication, blocking cellular receptors, and obstructing the function of viral proteins [62]. The cellular miRNA expression has an important impact on the regulation of viral replication by T lymphocyte involvement and response of defense mechanism to viral infections [63]. miRNAs can inhibit the viral translation after the attachment of miRNAs to 3' -UTR of the viral genome or target the receptors, structural or non-structural proteins of SARS-CoV-2 without affecting the expression of human genes [64]. Balmeh et al. downloaded the nucleotide sequences of 1872 miRNAs from the miRBase database. Forty-two miRNAs had the highest score, which mitigates the pathogenesis of COVID-19 disease via binding to the SARS-CoV-2 genome and inhibiting its post-transcriptional expression [65]. Chan et al. reported that mutations in SARS-CoV-2 3'-UTR lead to virus escape from the host immune system [66].

In the case of infection, the non-coding SARS-CoV-2 miRNA may interfere with normal cellular homeostasis by upregulating certain host mRNA levels generally controlled by the host miRNAs. Consequently, by down-regulating specific host miRNAs, the virus enhances its replication cycle and attenuates the host's immune

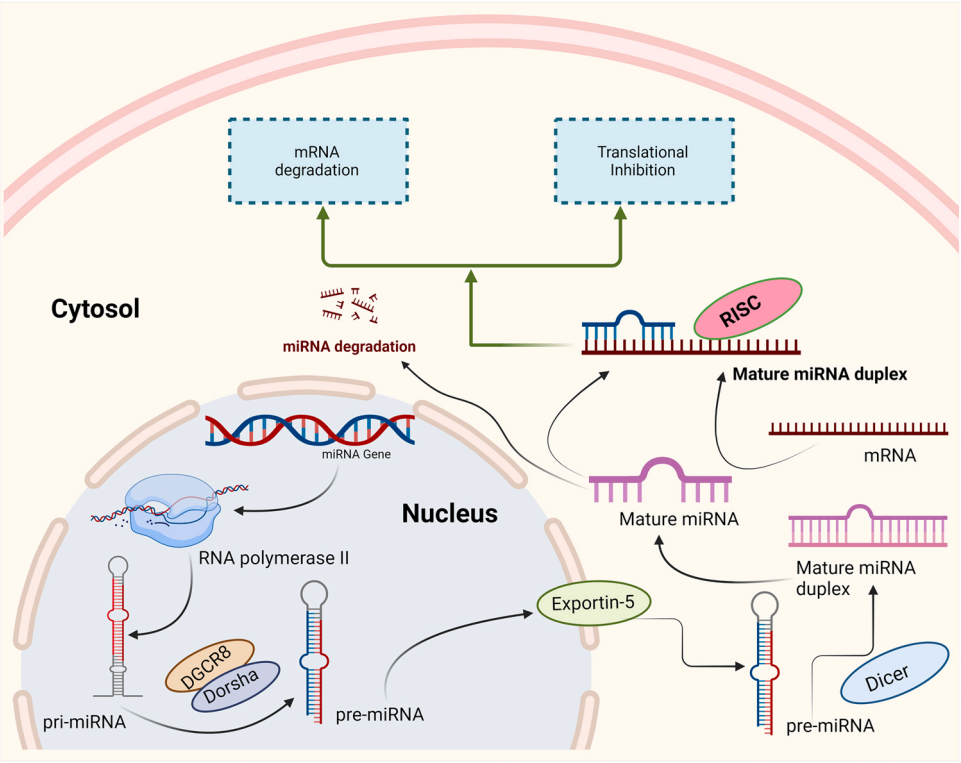

Fig. 2. miRNA biogenesis and post-transcriptional regulation of genes.

responses [67]. Bioinformatics analysis of the SARS-CoV-2 genome reveals potential miRNAs' binding sites in various genome regions, e.g., in the critical 5' UTR regions of ACE-2 (angiotensin-converting enzyme-2) or TMPRSS2 (transmembrane protease serine 2) [68]. On the other hand, viral miRNAs can also affect the expression of host mRNAs. They are involved in cell proliferation and survival, stress responses, and antiviral responses such as Toll-like receptors (TLRs) or cytokines such as type I IFN.

Upon entry into the host cell, SARS-CoV-2 releases its genomic RNA. Consequently, the host antiviral immune responses are attenuated. Alternatively, viral miRNAs can reduce virus replication in infected cells, allowing the host cells to survive, go into a latency state, and increase viral spread to other people in the population [69]. Some viral miRNAs target specific host mRNAs and miRNAs, thereby altering gene expression and modulating the pathways associated with the immune system. At the same time, host cells may change their own miRNA expression profile to defend themselves against the disease [70]. Therefore, miRNA will provide a practical concept to elucidate the infectivity and replication process of the current SARS-CoV-2 pandemic. Whereas SARS-CoV closely resembles SARS-CoV-2, many interactions have been established in their sign appearances presented by them. However, there are marked differences between diseases caused by both viruses [71]. An overview of the role of the SARS-CoV-2-miRNA on the host immune system activity that has been explored is shown in Table 1.

A study conducted by Mallick et al. in 2009 assessed the miRNA landscape in human bronchoalveolar stem cells (BASCs) was assessed at the time of infection with SARS-CoV, displaying the up-

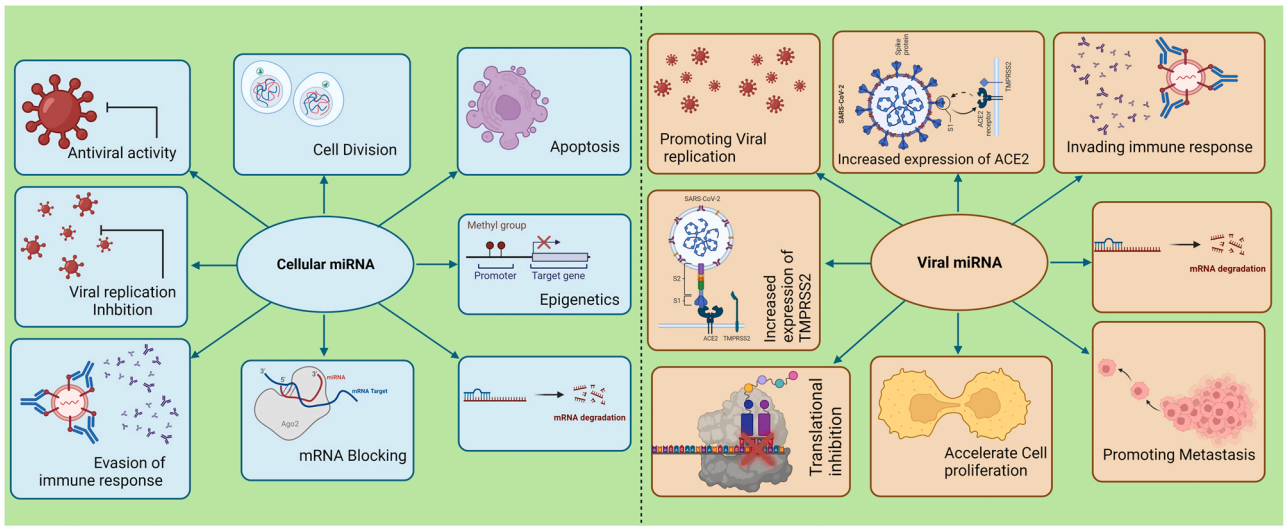

Fig. 3. Diagrammatic representation of the role of both cellular and viral miRNAs.

Table 1
An overview of the role of the SARS-CoV-2-miRNA on the host immune system activity that has been explored.

SARS-CoV-2-miRNA	Related process		Reference
miR147–3p	enhanced the expression of TMPRSS2	5' UTR	[81]
MR385–3p	Regulate T-cell activation and survival	5' UTR	[9]
MD2–5p,	reducing the host cell apoptotic, evasion immune system	5' UTR	
MR147–3p		5' UTR	
MD241–3 P	Pulmonary vasculature	5' UTR	[82]
MD3 – 3 P	Antiviral innate immunity, an inducer of apoptosis pathway during viral infection	5' UTR	
mir-D8–5p,	enhance viral replication, host cell survival and host immune evasion	ORF1ab- nsp6,	[83]
mir-R1–5p,	Evasion immune system	ORF1ab- nsp3	
miR-D6–3p,		ORF1ab-nsp4	
miR-D10–5p,		ORF1ab- endoRNase	
miR-D5–3p,		ORF1ab- nsp3	
miR-D11–5p,		ORF1ab-ribose methyltransferase	
miR-D14–3p,		ORF7a + ORF7b	
miR-D2–3p,		ORF1ab- nsp2	
miR-R3–3p,		ORF1ab-RdRP	
miR-R5–5p,		gene M+ ORF6	
miR-R6,		gene N (structural nucleocapsid phosphoprotein)	
miR-R4,		+ ORF10	
miR-R2,		ORF3a	
miR-D13,		ORF1ab- nsp3	
miR-D12,		gene M (structural membrane glycoprotein)	
miR-D9,		gene M (structural membrane glycoprotein)	
miR-D7,		ORF1ab- exonuclease	
miR-D4,		ORF1ab- nsp6	
miR-D3,		ORF1ab- nsp3	
miR-D1		ORF1ab- nsp3	
		ORF1ab- nsp2	

regulation of miR-17, miR-214, and miR-574–5p, that results in viral replication inhibition, and consequently, evasion of immune response before the virus has been successfully transmitted, in addition to the down-regulation of miR-98 and miR-223 to control the BASCs differentiation, proinflammatory cytokine activation and suppression of ACE2. It was also observed that S and N proteins in BASC down-regulate both miR-98 and miR-223 to influence many stages of the maturation process in these cells and enable inflammation-related cytokines to reduce the function of the ACE2 enzyme. Such a mechanism essentially forms the productive transmission and replication of viruses inside BASC, resulting in continuous degradation of cells of the respiratory tract and consequently damaging the repairing ability [72]. In general, this study revealed the various ways in which a virus utilizes cellular miRNA instruments to its advantage. Hosseini et al. have recently identified seven targets for miRNA in the SARS-CoV-2 genomic RNA. There were initially ten goals, but three of them were lost because of mutations that had been retained. "MiR-574–5p, miR-214, miR-17, miR-98, miR-223, and miR-148a" are those host miRNAs that are capable of annealing to encoding transcripts of the SARS-CoV-2; consequently, resulting in immune system mediation [73].

In addition, an in-silico study conducted by Fulzele et al. has identified around 873 miRNAs in the host targeting the SARS-CoV-2 strain, of which around 558 also target genomic genes in the SARS-CoV. Further illustrating that the miRNAs that have the top score of targeting the sequence are thus commonly expected to have definite target positions on the SARS-CoV-2 genomic RNA were "miR-15a-5p, miR-15b-5p, miR-30b-5p, miR-409–3p, miR-505–3p, and miR-548d-3p", according to their report [74]. These cellular miRNAs indicate potential antiviral activity on both SARS-CoV and SARS-CoV-2 viruses. Therefore, testing these miRNA in-vitro and in-vivo animal models would be essential for possible usage as a target as a therapy. Importantly, a recent study found that the number of circulating miRNAs from several tissues, including numerous established cardiometabolic indicators, increases with COVID-19 severity. MyomiR miR-133a and liver-derived miR-122 have been linked to 28-day mortality. MiR-133a is associated with inflammation-induced myocyte damage, whereas miR-122 is associated with the hepatic acute phase response. It has been suggested that future research is needed to determine whether miR-133a or miR-122 measurements have the potential to help in prognosis estimation by assessing organ damage and inflammation resolution, which might affect treatment decisions. As a result, it is intriguing to examine whether miRNA analysis during SARS-CoV-2 infection might be used as a diagnostic biomarker to predict illness severity. This can be used to offer the host with tailored therapy [75].

In coronavirus infection, cocktails of several miRNAs mimicking via the intranasal route would be beneficial. These human miRNAs efficacy against coronaviruses may help prevent any potential outbreaks. In an earlier analysis, cellular miRNAs-181 of the host bind to the ORF-4 region of the porcine reproductive and respiratory syndrome virus (PRRSV) viral genome to prevent replication of the virus. Furthermore, Guo et al. administered miR-181 mimics through intranasal inhalation to inhibit replication of the PRRSV in an experimental porcine model [76]. One more study used miR-130 mimic administration through intranasal inoculation to reduce the lethal effect of PRRSV on piglets [77]. Likewise, the intranasal inoculation of five miRNA mimics is chemically modified to protect against H1N1 replication in mice [78]. The role of cellular miRNA has been described in Table 2.

The binding position for miRNA predicted through the Computational approaches should be considered cautiously, as findings frequently were unsuccessful for experimental verifications. Such an increased false-positive number of the predicted site for the miRNA target has often been mentioned. However, specific methods, like multi-targeting, incorporation of current experimental data, or the usage of algorithms considered for refining the effects of miRNA target hunts [79], may be used to narrow it down. Conditions unique to the research question may also be helpful to consider ("e.g., excluding potential targets of all miRNAs that are not expressed in cells prone to SARS-CoV-2 infection".

Based on the Hosseini et al. studies [73] and Fulzele et al., such steps have been taken to refine the findings. Nevertheless, their results remain encouraging and must be considered for additional

Table 2
An overview of the role of the cellular-miRNA on the SARS-CoV-2 activity has been explored.

Cellular-miRNA	Related process	Reference
miR-17, miR-214, miR-574–5p	Viral replication inhibition, evasion of immune response	[72]
miR-98, miR-223	bronchoalveolar stem cells differentiation, proinflammatory cytokine activation, suppression of ACE2, immune system mediation	
miR-98, miR-223 miR-148a	bronchoalveolar stem cells differentiation, proinflammatory cytokine activation, suppression of ACE2, immune system mediation immune system mediation	[73]
miR-15a-5p, miR-15b-5p, miR-30b-5p, miR-409–3p, miR-505–3p, miR-548d-3p	antiviral activity	[74]
miR-181	inhibit replication	[76]
miR-130	reduce the lethal effect of PRRSV	[77]
miR-200, miR- 429, miR-200b, miR-200c	suppression in ACE2 expression, lowering the ACE2-facilitated infection	[84]
miR-155, miR-9	evasion of immune response	[85]
miR-6864–5p, miR-5197–3p, miR-4778–3p miR-530b-5p miR-32	antiviral activity Inhibit viral entry	[86]
miRNA-3154, miRNA-7114–5p, miRNA-5197–3p, miR-5197–3p, miR-17–5p, miR-20b-5p miR-21–3p, miR-195–5p, miR-16–5p, miR-3065–5p, miR-424–5p, miR-421, miR-1307–3p miR-124–3p miR-29b-3p, miR-29b-3p, miR-338–3p, miR-4661–3p, miR-4761–5p miR-4793–5p, miR-8066 miR-190a-5p	mitigate the pathogenesis, inhibit its post-transcriptional expression Viral replication inhibition block the assembly and production of viral particles evasion of immune response	[87]
miR-18	suppression in ACE2 expression	[88]
miR-146a	Regulate Toll-like receptors (TLRs) downstream signalling, regulate innate immune response	[89]
miR-4288, miR-6838–5p, miR-497–5p, miR-510–3p, miR-624–5p,	block viral RNA replication	[90]
miR-31–5p, miR-423–5p, miR-23a-3p	Viral replication inhibition	[91]
miR-26a-5p, miR-29b-3p, miR-34a-5p	antiviral activity	[92]
miR-6501–5p, miR-618, miR-183–5p, miR-627–5p, miR-144–3p	regulate the immune responses, Viral replication inhibition	[93]
miR-1–3p, miR-199a-3p, miR-20a-5p	T-cell differentiation and activation, Viral replication inhibition, evasion of the immune system	[94]
miR-4661–3p	antiviral activity	[81,87]
miR126–3p	regulating inflammation	[95]
miR-198, miR-622	Antiviral activity inhibit viral replication	[27]

studies on pathogenesis and possible miRNA therapy for Covid-19 [74]. Host and viral miRNA's biosynthesis and the role of miRNA in the host during COVID-19 infection has been illustrated (Fig. 3).

The suppressive of the SARS-CoV-2-encode miRNAs on these genes suggested that the possible role of the SARS-CoV-2-encode miRNAs on these genes suggested their potential role in reducing the host cell apoptotic to subvert host defense. Therefore, we also searched the targets of SARS-CoV-2 encoded miRNA on the 5′ UTR of human genes. The 11 virus miRNAs were identified to bind to the 5'-UTR of 13 target genes, including the binding between MR385–3p and TGFBR3 (Transforming Growth Factor Beta Receptor 3), a widely recognized gene expressed in cells of both the innate and adaptive immune system. It is reported to play a role in promoting Th1 differentiation and regulation of regulatory T-cell activation and survival. MR147–3p targets the enhancer of TMPRSS2 in the gut. Several studies have implicated the gastrointestinal infection of SARS-CoV-2 [9]. Fig. 4.

Furthermore, in recent research, the plasma miRNAs and cytokines profiles of COVID-19 and other community-acquired pneumonia (CAP) were compared. A preliminary screening and subsequent validation tests in a separate cohort of patients identified a pattern of 15 dysfunctional or dysregulated miRNAs in COVID-19 and CAP patients. Furthermore, multivariate analysis revealed that the conjunction of four miRNAs, namely, miR-106b-5p, miR-221–3p, miR-25–3p, and miR-30a-5p, substantially differentiated between the two disorders. The search for miRNA targets, along with plasma protein measurements, revealed a distinct cytokine signature between COVID-19 and CAP, which comprised EGFR, CXCL12, and IL-10. There were also significant changes in plasma levels of CXCL12, IL-17, TIMP-2, and IL-21R between mild and severe COVID-19 individuals. These findings shed light on the etiopathological pathways that characterize COVID-19. It is worth noting that the differential expression of suggestive miRNAs, in conjunction with specific cytokines, can determine the severity of COVID-19 illness [80]. As a result, miRNAs can not only be utilized as therapeutic regimens but also the used as reliable diagnostic indicators.

miRNAs and ACE2 receptor expression in SARS-CoV-2 infection

ACE2 is known to aid in maintaining blood pressure and the balance of electrolytes in the body. Similarly, it also lowers the amount of circulating Angiotensin II through suppression of the renin-angiotensin-aldosterone system with the activity of anti-hypertension. Lately, ACE2 has been identified as a target receptor for the spike protein of SARS-CoV-2 and shows essential roles throughout the COVID-19 infection [96]. Notably, many other medical conditions, like cardiovascular system diseases, diabetes, and asthma, also tend to affect COVID-19 patients with severe symptoms [84]. It is important to remember that ACE2 is expressed in cardiomyocytes, and the expression level is increased in hosts suffering from heart illnesses. Therefore, the level of SARS-CoV-2 infection may become the level of SARS-CoV-2 infection may become further prominent through ACE2 in patients with comorbidities, which sequentially might lead to further myocardial harm. Some studies have stated that miRNAs might potentially control ACE2 expression in many types of cells and under disease circumstances. However, there is still a scarcity of clinical trials to provide a vivid image of miRNAs' potential to develop effective and reliable therapeutic regimens against COVID-19 [26–97]. ACE2-associated miRNAs, in particular, should be carefully explored since ACE2 is the essential factor that requires more focus owing to its association with the viral agent, which can be SARS-CoV or SARS-CoV-2 [98,99]. As a result, it has been suggested that the clinical manifestations of certain ACE2-associated miRNAs, such as miR-18, miR-29, and miR-125b, be thoroughly investigated in order to find novel miRNA-based therapies for COVID-19; specifically, it is presumed that the use of anti-miR-18

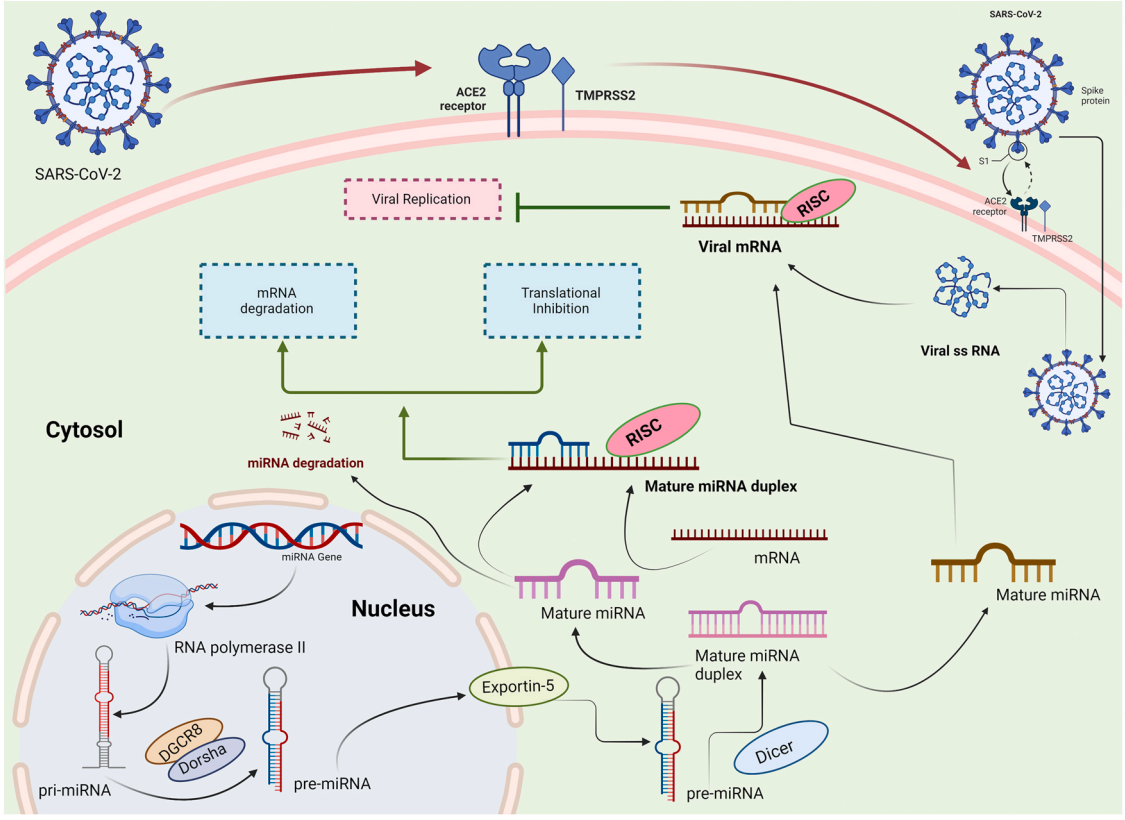

Fig. 4. The host and viral miRNA's biosynthesis and the role of miRNA in the host due to COVID-19 infection.

and anti-miR-125b may be beneficial in treating COVID-19-related nephropathy [88,100].

The miR-200 is considered a family of several miRNAs that also include miR- 429, miR-200b, and miR-200c. These are well-recognized miRNA families that are highly studied in anti-cancer research [30]. Likewise, it has been revealed that the miR- 200c level is up-regulated in cardiovascular diseases [100]. In a study performed by Lu et al. to investigate the miR- 200c Role in SARS-CoV-2, it was found that increased expression of miR- 200c induced suppression in ACE2 expression in both human and rat's cardiomyocytes. Moreover, has suggested more investigation to study the possible miR-200c role in lowering the ACE2-facilitated infection of human-induced pluripotent stem cell-derived cardiomyocytes by SARS-CoV-2 or SARS-CoV-2 spike pseudotype viruses are acceptable. Nevertheless, bearing in mind that the association of miR-200c and cardiovascular diseases, together with the up-regulation of miR-200c, must be cautiously examined [30].

In a recent study, researchers looked at the blood levels of soluble ACE2 (sACE2) and four microRNAs (miR-421, miR-3909, miR-212–5p, and miR-4677–3p) in COVID-19 patients and compared them to clinical and pathological variables [101]. Irrespective of gender, diabetes condition, or obesity, sACE2 levels were elevated in COVID-19 individuals. Additionally, the four miRNAs studied were elevated in COVID-19 patients and were found to be positively associated. Likewise, sACE2 was strongly related to miR-421, miR-3909, and miR-4677–3p, indicating a significant relationship between these markers. MiR-212–5p was shown to be increased exclusively in moderately infected patients. Additionally, it has been found as unique in the case of male and non-obese COVID-19 patients. MiR-212–5p was shown to be connected with D-dimer, which has an important prognostic marker in severely infected COVID-19 patients. Whereas sACE2 was found to be positively correlated with coagulation tests such as aPTT and platelets, showing their usefulness as coagulopathy indicators in patients with COVID-19. In diabetic COVID-19 patients, there was also a significant connection between sACE2 and C-reactive protein (CRP), suggesting that this marker may have a role in their inflammatory condition. Interestingly, laboratory tests of COVID-19 patients revealed that sACE2 and its regulatory miRNAs were elevated and associated, demonstrating their clinical significance as biomarkers in COVID-19 disease [101].

Furthermore, Sodagar et al. showed that different kinds of miRNAs could affect the progression of various lung illnesses by targeting distinct pathways and genes. Increased levels of miR-200c are expected to contribute to reduced ACE2 production, which might increase the risk of infection, inflammation, and coronavirus illness sequelae [102].

Besides ACE2 receptors, SARS-CoV-1 entry necessitates cellular proteases to bind viral Spike protein, which leads to cleavage of Spike protein at the S1/S2 position, and the S2' position permits fusion of both viral and cellular membranes; this is process is motivated by the cleaved S2 subunit of the spike protein. The Spike protein of SARS-CoV binds to ACE2 as the entry receptor and hires the transmembrane protease serine 2 (TMPRSS2) for S protein priming [103]. Similarly, SARS-CoV-2 employs the TMPRSS2 for Spike protein priming and virus-host cell membrane fusion followed by cell entry. This is suggested as another target for antiviral development therapeutics [104]. Matarese et al. researched TMPRSS2; they found that the expression of TMPRSS2 in human endothelial cells is regulated and lowered through miR-98 by attaching to 5UTR TMPRSS2 mRNA [105].

Furthermore, because TMPRSS2 is another critical element of SARS-CoV-2 viral entry, inhibiting it could help to alleviate COVID-19 [96]. In human endothelial cells separated from the lung and the umbilical vein, miR-98–5p controls the expression of TMPRSS2, indicating that it might be used in miRNA-based COVID-19 therapies [105]. Some other report predicts that hsa-miR-32, hsa-miR-98, and hsa-miR-214 can suppress the synthesis of TMPRSS2, which might open the way for further research into the potential therapeutic effects of hsa-miR-32, hsa-miR-98, and hsa-miR-214 against SARS-CoV-2 [106]. Interestingly, hsa-miR-32 has been found study; hsa-mir-32 was shown to strongly suppress the expression of TMPRSS2 in Caco-2 cells, indicating that future studies must concentrate on hsa-miR-32 [106,107].

However, it would be worthwhile to investigate if miRNAs may limit the synthesis of structural and non-structural proteins involved in critical phases of the SARS-CoV-2 life cycle, including spike protein and non-structural proteins such as Nsp1, Nsp4, and Nsp12, and envelope (E) proteins [108]. Earlier studies on the SARS-CoV found that several miRNAs such as miR-17*, miR-574–5p, and miR-214 may target various proteins of the viral machinery, including S, E, and membrane (M) proteins. Additionally, ORF1a has been found to be associated with these miRNAs [72]. Interestingly as we are all aware that SARS-CoV and SARS-CoV-2 have a significant genetic similarity [109]; hence antiviral effects of such miRNAs, including miR-574–5p and miR-214, can be exploited to alleviate the COVID-19 symptoms [99].

Potential risks and side effects

Anti-inflammatory and antiviral miRNAs may be more effective when used together than when used alone. Meanwhile, targeting the viral genome, critical proteins, or miRNAs as an antiviral method for developing effective therapeutics against COVID-19 could be a promising alternative [9,110]. However, a single miRNA can affect many target mRNAs; excessive doses of a single miRNA can have substantial off-target consequences under in vivo conditions. As a result, employing a system biology approach for combinatorial therapeutics may involve a smaller dose of a cocktail of therapeutically critical microRNAs to eliminate SARS-CoV-2 without any side effects [9].

The key problems of miRNA-based therapy are targeted delivery, instability, and toxicity [9,111] ; hence adequate carrier vehicles are required for successful and effective delivery of miRNAs to the sites of infection. In this context, investigations have demonstrated that mesenchymal stem cells (MSCs) have a preference for lesion or inflamed areas [9,112,113], suggesting that they could be employed to reduce the cytokine storm [9] and hence may reduce the inflammation in the lungs caused by SARS-CoV-2. Cytokine storm is an important aspect of the SARS-CoV-2 infection and has been suggested as a leading cause of death in patients with COVID-19. So, mitigating the deleterious consequences of exaggerated secretion of cytokines by miRNA therapeutics while bypassing the side effects of this approach can be a significantly efficient therapeutic regimen to treat COVID-19.

Conclusions and future prospective

Several cellular processes, including infection with RNA viruses, are regulated by miRNAs. In order to create a proviral environment that improves replication of the virus and propagation inside the host cell, RNA viruses could control the level of certain miRNAs inside the cell. Furthermore, changes in miRNA levels following viral replication are an essential component of the host response to infection, sculpting both the activation stages and the antiviral response resolution processes.

Many studies have revealed that miRNAs are involved in diverse and complex processes during the infection process of SARS-CoV-2. The virus modifies the infected host's cellular miRNAs during infection, which leads to increased viral replication and enhanced assembly of viral particles. On the other hand, cellular Non-coding RNAs, including miRNAs, act as an essential antiviral immunity component by controlling the expression of ACE2 receptors, hence reducing the viral entry into the host cell. In addition, the interaction

of cellular miRNAs with RISC proteins can cut down and silence the viral RNA. The degradation of viral RNA, along with reducing the expression of ACE2 receptors, can substantially reduce the viral load. Genetic alterations in the miRNA binding sites of the viral genome can increase pathogenicity by allowing the virus to avoid RNA degradation and silencing by cellular miRNAs. One of the hopeful methods of treating the SARS-CoV-2 infected host using non-coding RNAs (ncRNAs) is the induction of small interfering RNA (siRNA) -mediated through passing synthetic complementary siRNAs to viral RNA sequences into infected host cells.

Further refinement of this principle requires elaborative studies, which can help in the generation of potential siRNA from ncRNAs that can target the viral genomic RNA. Likewise, antiviral therapies that use miRNAs, such as vectors in vaccinations or gene therapy, have been proposed. Furthermore, the miRNAs involved in the regulation of ACE2 receptors require more attention and extensive investigations as this strategy can be employed as an effective therapeutic regimen against COVID-19.

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CRediT authorship contribution statement

Jivan Qasim Ahmed: Conceptualization, Data Curation, Writing – original draft, Writing – review & editing. **Sazan Qadir Maulud:** Writing – original draft, Writing – review & editing. **Manish Dhawan:** Conceptualization, Data curation, Writing – original draft, Writing - review & editing. **Priyanka:** Writing – original draft, Writing – review & editing. **Om Prakash Choudhary:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing. **Paywast Jamal Jalal:** Writing – original draft, Writing - review & editing. **Rezhna Kheder Ali:** Writing – original draft, Writing – review & editing. **Gahin Abdulraheem Tayib:** Writing - Original Draft, Writing - review & editing. **Dlshad Abdullah Hasan:** Writing – original draft, Writing – review & editing. All authors critically reviewed and approved the final version of the manuscript.

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Declaration of competing interest

All authors report no conflicts of interest relevant to this article.

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