Review

Micro-RNAs in the regulation of immune response against SARS CoV-2 and other viral infections

Tareq Abu-Izneid a, Noora AlHajri b, Abdallah Mohammad Ibrahim c, Md. Noushad Javed d, Khairi Mustafa Salem a, Faheem Hyder Pottoo e, Mohammad Amjad Kamal f,g,h,*

a Pharmaceutical Sciences, College of Pharmacy, Al Ain University, Al Ain, Abu Dhabi, United Arab Emirates
b Department of Epidemiology and Population Health, College of Medicine, Khalifa University, United Arab Emirates
c Fundamentals of Nursing Department, College of Nursing, Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 31441, Saudi Arabia
d Department of Pharmaceutics, School of Pharmaceutical Education and Research (SPER), Jamia Hamdard, New-Delhi, India
e Department of Pharmacology, College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, P.O. Box 1982, Dammam 31441, Saudi Arabia
f West China School of Nursing/Institutes for Systems Genetics, Frontiers Science Center for Disease-related Molecular Network, West China Hospital, Sichuan University, Chengdu 610041, Sichuan, China
g King Fahd Medical Research Center, King Abdulaziz University, P. O. Box 80216, Jeddah 21589, Saudi Arabia
h Enzymoics, Novel Global Community Educational Foundation, 7 Peterlee Place, Hebersham, NSW 2770, Australia

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Abstract

Background: Micro-RNAs (miRNAs) are non-coding, small RNAs that have essential roles in different biological processes through silencing genes, they consist of 18–24 nucleotide length RNA molecules. Recently, miRNAs have been viewed as important modulators of viral infections they can function as suppressors of gene expression by targeting cellular or viral RNAs during infection.

Aim of review: We describe the biological roles and effects of miRNAs on SARS-CoV-2 life-cycle and pathogenicity, and we discuss the modulation of the immune system with micro-RNAs which would serve as a new foundation for the treatment of SARS-CoV-2 and other viral infections.

Key scientific concepts of review: miRNAs are the key players that regulate the expression of the gene in...
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Introduction

The COVID-19 is a viral respiratory infection that is caused by the newly discovered virus SARS-CoV-2, the virus is known to have appeared initially in Wuhan wet animal market, China by December 2019 and later spread worldwide [1], it was recognized by the WHO as a pandemic in March 2020. Nowadays, the number of positive cases that are diagnosed with the disease exceeds 13 million, with over 550 thousand deaths reported which accounts for around 4% fatality rate [1]. SARS-CoV-2 is a member of the family of Coronaviridae and the subfamily Coronavirinae in which there are 4 different genera: the alphacoronavirus, betacoronavirus, gammacoronavirus, and delta coronavirus. Coronaviruses are single-stranded positive-sense RNA (+ssRNA) with a length of the genetic material of 30 kb, considering the length of its genetic material, the SARS-CoV-2 is the largest RNA virus [2]. The RNA of the virus is used for the translation first of the polyprotein 1a/1ab (pp1a/pp1ab) [2], then the polyprotein undergoes cleavage by protease and papain-like protease to form the nonstructural proteins (NSPs) [3]. The NSP will form the replication-transcription complex (RTC) in a double-membrane vesicle (DMVs) [4]. After that, a subgenomic RNAs (sgRNAs) is formed by RTC [5]. The sgRNAs serves as templates for the production of the subgenomic mRNAs [5]. Coronavirus usually contains 10 open reading frames ORFs [6]. The first ORF is (ORF1a/b), which is the largest and contains around two-third of the genetic material [7]. The first ORF includes the code of 16 nsps [8]. The remaining ORF encodes the four structural proteins which are: spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins. Also, it contains other accessory proteins that differ between each type of coronaviruses like 3a/b protein, and 4a/b protein, HE protein [2]. The functions of 4 structural proteins are: Homotrimer of S proteins gives the spikes on the surface of the virus which serve as the attachment part to the host cell [9]. The M protein with 3 different domains gives the shape to the virus, facilitating the curvature of the membrane, and is responsible for viral binding to the nucleocapsid [10]. The E protein is essential in the viral pathogenesis and has an important function for viral assembly and release [11]. The N protein has 2 different domains which can bind to RNA, it binds to ns3 to link the viral genome to the RTC. Also it helps in the packaging of the genome into the virions. It is reported that the N protein has an antagonistic effect for the interferon, which enhances viral replication [12] (Fig. 1).

Pathophysiology of SARS-CoV-2

Transmission from person to person is via infected air droplets or direct contact; the incubation period of the virus is around 6.4 days [1]. After it enters into the respiratory system, the life cycle of the virus begins which consists of 5 stages [13], the attachment of the virus to the host cell via binding to the ACE2 through the spike protein [14]. The ACE2 receptor is found in several tissues like the lung, kidney, heart, bladder, and the GI system [15]. After the binding, the spike protein is cleaved in the two-step process to be activated. The cleavage of the S protein occurs at the S1/S2 site of the protein that would be primed and cleaved in the next step at the site S2 in order to be activated [16]. The spike protein of the coronavirus is considered unique protein among the viruses because it has several proteases to cleave it [17]. Once the spike protein is activated it will be fused with the cell membrane, which represents the second stage of the viral replication, which is the fusion or the penetration [17]. Transcription and biosynthesis of viral proteins is the third step in the replication of SARS-CoV-2, the last two steps of the virus life cycle are the viral maturation and the release of the viral particle [13].

ACE2 is found on the apical site of lung epithelium, the entry of the virus to the lung tissue causes destruction of cells and lung injury [18]. The 3 types of cells that have the initial innate immune response to viral entry are the epithelial cells, lung macrophages and the dendritic cells [19]. The phagocytosis of virally infected cells by the macrophages and dendritic cells results in presentation of the antigen to the T cells via antigen-presenting cells, which leads to T cell activation and the beginning of adaptive immune response [13]. The strong inflammatory response that is associated with the viral infection could result in Acute respiratory distress syndrome (ARDS) [20]. The mechanism that mediates the ARDS is believed to result from the cytokine storm in which a large number of cytokines and proinflammatory mediators are released by the immune cells [21].

The alveolar damage that is caused by the virus will be followed by edema of fibrin exudate, then hyperplasia of the pneumocyte type II. In some severe cases, there is a thickening of the alveolar sputum causing hyaline membrane formation. The pneumocyte type II is the target for the virus because of the expression of ACE2 receptor on its surface, those cells are responsible for the surfactant production and they share the same basement membrane with adjacent endothelial cells [22]. In severe cases, it is observed to cause acute myocardial cells injury as evidenced by an increase in cardiac troponin in 28% of the severe cases, especially if the individual has a pre-existing cardiac disease. The cause of myocardial cell injury is yet to be explained, but different theories have been proposed, it might be due to cytokine effect from the cytokine storm or direct infection by the virus although there is no evidence of signs and symptoms of myocarditis [23]. Also, Thromboembolic events are reported: DIC is found to be linked with mortality in severe COVID-19 cases, it is believed that DIC results from both arterial and venous thrombosis [24]. According to one German study, the incidence of venous thromboembolism was 27% and arterial thrombosis is 4% in cases who were admitted to ICU, half of the cases with VTE were found to develop pulmonary embolism, which complicates the respiratory status [25]. An autopsy showed large thrombosis in pulmonary vessels, the thrombosis is found in areas that have inflammatory changes [26]. The percentage of Gastrointestinal system involvement is around 17.3% according to cohort study [27], the virus can infect the epithelium of the gas-
trointestinal tract directly through the ACE2 receptor. GI symptoms can range from anorexia, nausea, vomiting and non-bloody diarrhea [28].

Introduction to miRNA

RNA interference or abbreviated as (RNAi) is a pathway that regulates genes [29]. microRNA (miRNAs) are small non-coding gene sequence that exists in most eukaryotes, they are 20–22 nucleotides, miRNA are part of the RNAi machinery [29,30]. The function of miRNAs is the silencing of RNA and post transcription regulation of gene expression [31,32]. miRNAs are found to have control on a wide range of genes which control biological activity like cell division, cellular differentiation, and death (apoptosis) [30]. miRNAs have a significant role in viral replication and can be utilized by the infected cells to control the replication of the virus [33]. Several viruses can express miRNAs like herpes virus and retrovirus. Recently, the identification of some genes that are regulated by viral miRNAs raised the suggestion that targeting those genes could have a role in controlling viral infection [33]. One study examined miR-122 in the treatment of chronic hepatitis c in chimpanzees, they found it causes a long-lasting suppression of the virus and improvement in the pathology [34]. Those pieces of evidence could raise the possibility that miRNAs could be a potential therapeutic option in the management of SARS-CoV-2. Several attempts have been conducted to evaluate the ability of this approach in treating and controlling COVID-19. One study used the computational approach utilizing the miR target program to match miRNA to coronavirus and evaluated the interaction between the miRNA and the mRNA of the virus using characteristics such as the free energy, the position of the binding sites in the 3’UTr and 5’UTR, and the scheme of the interaction between the nucleotides [35]. They found 7 complete complementary miRNA (cc-miRNA) that matches for SARS-CoV-2 that can bind to the location that encodes for ORF1ab, S,N [35]. They proposed that the concentration of cc-miRNA that used can suppress the viral mRNA without having a significant effect on the human genome [35]. Another paper evaluated 2565 miRNA for their ability to bind the gRNA of the coronavirus, their result revealed that miR5197-3p can bind SARS-CoV-2, interestingly, the binding site of the cc-miRNA of the coronavirus cannot target genes of the humans, which means there are fewer side effects of the translation of the human mRNA [35]. Furthermore, another computational study found that virus miRNA has greater regulation of the biological process of the immune response and the cytoskeleton, which could create a greater effect on the viral life cycle [36].

Effect of cellular/host miRNAs on viral replication and pathogenesis

Knowing fact that miRNAs play essential roles in gene regulation in mammals, therefore miRNAs directly or indirectly affecting virus ability to replicate and to cause infection [37]. During viral life cycles (Infection processes), in an infected cell with RNA viruses, cellular miRNAs are expected to bind virus mRNA (virus genomes), and thus altering host mRNA stability, reducing translation of the viral genome, and/or changing the levels of free miRNAs in the cell [38]. This effect may help the viral transcripts to be more stable and alter the host cell genome expression [39]. Several reports revealed that miRNAs are involved in viral pathogenesis process by inducing alteration in the host immune system against the virus, promoting viral replication, or altering miRNA-modulated host gene regulation [38].

It is well reported in the literature that miRNAs levels and types of expression, biogenesis and sequestration, are changed during coronavirus infection as a response from the host as well as viral manipulations. Determination and analysis of miRNA expression during coronavirus infections showed 10–100 s of miRNAs levels
are changed by different types of coronaviruses. Thus, miRNAs could be considered as potential biomarkers during coronavirus infection [37,40]. Gottwein et al. have compiled up to date data on what is known about cellular miRNAs and their effects on viral replication and pathogenicity [37]. Understanding mechanisms and functions of miRNAs during SARS-CoV-2 infections would significantly contribute to the process of developing therapeutic option based on miRNA that will act by either as; miRNA mimics and/or miRNA antagonists [41].

**Effect of cellular miRNAs on the virus life cycle and pathogenesis**

As discussed above, miRNAs of either cellular or viral origin could positively or negatively affect the viral life cycle and replication. They can affect host physiological processes, including the immune system [37]. Viruses generate miRNA to facilitate virus-induced cytopathy and pathogenicity [42]. Additionally, the host miRNA expression level/type was found to be affected by viral infections [39]. There is evidence in the literature that cellular miRNAs can bind to various types of viral RNA and thus directly regulate viral infectious progress [38]. Given the fact that the structure of the genetic material for the positive-strand RNA viruses mimics the cellular miRNAs genomic structure, this will allow for the miRNA to bind directly to the viral RNA, and this could result in upregulation or downregulation of the viral replication. The known mechanisms of how Micro-RNAs (miRNAs) affect RNA-viruses, including SARS-CoV-2, replication are wide-ranged. They could inhibit SARS-CoV-2 replication by:

1. Direct-Acting by Targeting Viral RNA: Host/Cellular miRNAs directly interact with the viral RNA.
2. Indirect-acting by modulating immune-pathogenesis process/response. Affecting the IFN-α/β signalling cascade process [41].

**Direct targeting of viral RNA (Direct host miRNA/viral RNA interactions)**

It is reported in the literature that human miRNAs can bind indirect way to the genome of the virus in both regions the coding and the non-coding 3’UTR regions resulting in translational repression and therefore producing antiviral effects [43]. Literature evidence also indicated that host-miRNAs bind to viral-RNA, regulating its translation, virus replication and thus affecting viral pathogenesis [38]. The underlying mechanism for host miRNAs-Viral RNA interactions is facilitated by the presence of micro-RNA Response Elements (MRES), that are in general found in the 5’UTR, coding region (CDS) and 3’UTR of the virus genetic material [41,44]. These interactions have been identified by the following outcomes that viral replication directly alters:

- a) Host miRNA binds to the 3’-NTR of viral-mRNA, resulting in suppression of viral translation or enhanced RNA viral translation.
- b) Host miRNA binds to the coding region of viral-mRNA, resulting in suppression of translation of the viral genes that prevent viral replication.
- c) Host miRNA binds to the 5’-NTR of viral-mRNA, resulting in stabilization of virus RNA and therefore enhancing replication (Fig. 2).

The three mechanisms regulate RNA virus replication inside certain type of cells and/or tissues [40,45]. There is a high degree of similarity that has been seen between SARS coronavirus (SARS-CoV) and SARS-CoV-2 [40].

To date, a limited number of cases where the viral infection was regulated by direct binding of miRNAs to the genome of the virus has been reported [38]. The reason behind this would most likely be justified as the virus would respond to the consequences of this interaction, and those are quickly removed. This justification was backed up by the accumulated findings which showed that most of the interaction between viral RNA and host miRNA leads to positive effects on the replication of the virus [38].

The following miRNAs; miR-323, miR-485, miR-491, miR-654, and miR-3145, are examples of host miRNAs which are reported to have an inhibitory effect on viral replication. This antiviral activity of these mi-RNAs was induced after they bound to the coding region of the influenza virus PB, which resulted in the degradation of the virus RNA thus suppression of viral translation and replication [43]. On the contrary, miR-122 is one of the reported miRNAs that showed a positive effect on viral replication (increased viral replication). Host miR-122 works by direct miRNA-virus interaction with the hepatotropic virus (HCV is a positive-sense ssRNA genome), leading to increased viral RNA accumulation/increase virus replication [38]. Based on this reported evidence, Fulzele et al. recently conducted *in silico* evaluation of host miRNAs targeting SARS and SAR-CoV-2. They found that 848 miRNAs could target the SARS genes and 873 miRNAs could target the SAR-CoV-2 genes. 558 miRNAs from the total number of miRNA that could target SARS (848) are commonly present in all SAR-CoV-2. Interestingly, 315 miRNAs are unique for SAR-CoV-2 and 290 miRNAs unique to SARS [43].

Viral miRNAs could go under selective pressure to avoid Host miRNA–virus interactions to abundant the antiviral activity of cellular miRNAs. Therefore, the level of achievement of such interactions could be maintained or revoked according to the ability and flexibility of the viruses to rapidly change/reshape their genomic structure as a response of the selective pressure. Finally, the amount and type of the miRNA within cells which are infected is expected to indirectly change during virus infection, due to the different mechanisms/process that is used to promote or reduce viral replication and are regulated by cellular miRNAs [37]. Therefore miRNAs have been used as biomarkers that can aid in the diagnosis and the prediction of the prognosis for some diseases including cancer and viral infections.

Several reported studies, which were conducted on bronchoalveolar stem cells (BASC) infected with SARS, have demonstrated that there are significant relationships between viral effects on miRNAs expression and the immunopathogenic responses during BASC infections [46]. In another study, the use of miR-200c-3p during SARS infection (miR-200c-3 pacts by binding to the 3’-UTR-mRNA in ACE2 cells) resulted in dysregulation of angiotensin-converting enzyme ACE2 expression and therefore suppressed viral infection by SARS and by other viruses that promote acute respiratory syndromes [46].

**Indirect effect by regulation of cellular miRNAs and cellular/host factors**

Besides the direct action of host miRNAs, viral miRNA, in regulating viral replication, indirectly actions are also reported [47]. The indirect action of miRNAs is to increase the expression of some cellular factors (in the host cell) that are essential for one or more stages in the viral life cycle [47]. It also involves the modulation of cell-surface receptor expression that is essential for viral entry and affecting tropism, and some cofactors that are required for translation and viral replication. Finally, miRNAs also affect the immune response to the infection such as induction of apoptosis (Fig. 2).

miRNAs modulation of immune-pathogenesis responses to viral infection is one of the most-known indirect effects, which leads to suppression of the interferon (IFN-α/β) signalling cascade or upregulation of the IFN-α/β production [41]. This virus-mediated alter-
ation in miRNA levels leads to a proviral or an antiviral environment [38]. Examples on this are miR-466i and let-7b are reported to act on type I interferons, IFNα and IFNβ respectively. Targeting these type I interferons by these miRNAs may cause loss of the antiviral state and some other cases prevent the translation of some pro-inflammatory cytokines such as IL6 [48]. miRNAs could also enhance or restrain the expression of some cell-surface receptors which are essential for viral entry and endocytosis such as CD4+ in the case of HIV and ACE2 in the case of SAR-CoV-2 [38,49]. miRNAs are most proficient at attacking SARS-CoV-2. In conclusion, miRNAs, for both viral and cellular origin, may act by direct and/or indirect mechanisms during viral infections, and this in its turn may have positive or negative consequences on viral replication, pathogenesis and cytopathology. The understanding these mechanisms would promote miRNAs as promising and potential targets for creating miRNA-based therapeutics for the treatment of COVID-19.

**Introduction to innate and adaptive immunity**

The immune system is divided into two large groups: the innate immune system and the adaptive, immune system. Together they work closely and take on a wide range of tasks at different levels.

*The innate immune system*

The Innate immune system is the initial mechanism of defense to counter foreign pathogen and is accounted for the inciter of a series of heterogeneous inflammatory reactions [50]. These inflammatory reactions are stimulated by pattern recognition receptors (PRR) which react to pathogen-associated molecular patterns (PAMP). PRR are grouped in 5 categories of receptors: Nod-like receptors (NLR), C-type lectin receptor (CLRs), RIG-like receptors (RLRs), Toll-like receptors (TLRs), and AIM2-like receptors (ALR) [51,52]. These receptors are critical in the regulation of the innate immune system and activation of other pro-inflammatory interferons and cytokines stimulated genes [53]. Recent advances in research provide evidence that several miRNAs plays role in the control of acute inflammatory, namely miR-155, miR-146, and miR-223 subsequent to pathogen recognition (Table 1).

**Adaptive immune system**

The adaptive immune system is mainly characterized by stimulation and clonal expansion of T- cells and B- cells. This stimulation and expansion result in the formation of antibodies in response to infection along with cytotoxic effect or response [54]. miRNAs have been widely associated with regulating the innate and adaptive immune system by modulating series of the immune response such as the maturation, stimulation, survival, and proliferation of T-cells and B-cells [55].

**miRNAs in the modulation of an immune response against viruses**

miRNAs are a new class of evolutionary small non-coding RNA (snc-RNA) molecules with an estimated size of 22 nucleotides (nt) [69]. miRNAs regulate gene expression post-transcriptionally by the formation of incomplete base-pairs and attaching to sequences in the 3’ untranslated region (UTR) of genes [70]. Consequently, this could either induce gene degradation or repress gene translation thus preventing protein accumulation. Given that miR-
miRNAs are capable of influencing critical proteins and molecules involved in signalling pathways and can target transcription factors with robust regulatory effect on the immune response [71,72]. It was determined that miRNAs have a significant role in immune system activation and cellular differentiation. More recently, miRNAs have been shown as a novel class of regulators of various immune and biological responses such as signal transduction, apoptosis, carcinogenesis, biogenesis, cell growth and development and even responses to viral infection. Moreover, miRNAs are involved in the control of Natural Killer (NK) cells stimulation, function and survival, and has demonstrated an ability to delete Dicers or Dgcr8 conditionally [73]. More specifically, in mice, it has been shown that miR-150 is crucial in the regulation of maturation and development of NK cells, while the miR-181 is responsible for human NK cells maturation, activation and function by activating Notch signalling [74]. Further, when mouse NK cells were treated with IL-15, this resulted in an alteration in the expression of numerous miRNAs [75]. Among miRNAs, when miR-223 was down-regulated, it was found that there was an upregulation of its target gene, granzyme B [75]. Also, it has been shown that when miR-155 is properly regulated, it can produce protective immune effects, while when miR-155 is deregulated it could stimulate malignant transformation [76]. Significant research findings by Dickey et al. and others have suggested that miR-155 is an important oncogene in chicken lymphomas [77] and was, later on, found that it is also expressed in abundance in mammalians with hematopoietic cancers, thereafter, it was classified as immunoregulatory noncoding RNA in macrophages and B lymphocytes [78–82]. These crucial discoveries elucidated that miR-155 is regulated by and plays a significant role within heterogeneous types of the active immune cells that include different types of T and B cell types, dendritic cells and NK cells. Moreover, evidence has shown that miR-155 expression is increased during the activation of T-cells, B cells, dendritic cells, and macrophages [73]. Additionally, miR-155 regulates the expression of numerous protein and signalling molecules that have a role in controlling the immune response such as Ship1 [73] and Socs1 [83], as well as transcriptional modulators such as Jarid2 [84], Ets1 [85], PU.1 [86] and Fosl2 [87]. Corresponding to its established roles on modulating the immune response, several types of research have revealed that miR-155 is critical in activating and controlling the immune response to viruses [53,88,89].

In an experimental study done by Trota et al. to assess the effect of miRs-155 on human NK cells that were infected by lentivirus in vivo, they observed that the NK cells which have been activated by IL-12 and IL-18 had an increased expression of miR-155, also they observed an important correlation between IL and 18 with and the levels of miR-155 and IFN-γ. Thus, it was proposed that miR-155 might play a role as a stimulator of IFN-γ production and when the miR-155 expression was down-regulated, there was a decline in IFN-γ levels. IFN-γ is a prototypic cytokine that is secreted by NK cells and they have an important role in controlling the immune response to viruses [53,88,89].

Given miR-155 have demonstrated an important role in tailoring CD4+ reactions in models of autoimmunity, thus, several papers on viruses and immune response highlighted the importance of miR-155 in intensification the responses of CD8+ T cell [90–92]. Furthermore, numerous researches observed that miR-155 is essential for ample CD8+ T cell activity, cytokine secretion, proliferation, and control of inflammation. The results of these reports enforce the significance of miR-155 in optimizing immune response after viral infection [90–92]. Moreover, several reports shed the light on the other aspects of the role of miRNAs as critical controls of the interaction network between host-pathogen. Although the involvement of several miRs could be part of a host defense reaction to limit the replication and proliferation of microorganism [93]. Interestingly, the host miRNAs pathway could be also manipulated by the viruses to facilitate pathogen replication and dissemination. These observations support a model where miRNAs could be used to target viral gene expression, control inflammation and modulate immune activity.

### The role of miRNAs in modulating the immune system against SARS-CoV-2

In general, miRNAs are also involved in regulating several other physiological conditions and biological pathways such as cell development, maturation, differentiation, proliferation and activation [94]. miRNAs are important regulatory mechanisms by which cells can eliminate undesired or malformed mRNA. Although miRNAs can be an important anti-viral tool within the host system that can activate the innate and adaptive immune responses, it found that miRNAs can also act as a gateway for the penetration of the virus because of its non-antigenic characteristics [95]. Several studies have shown that viruses could utilize the machinery of the host to process the miRNAs and modulate host immune system.
response [38,96,97]. Interestingly, this can uniquely modulate cellular pathways that override the host’s defense system [96]. SARS-CoV-2 belongs to coronaviridae family and have been shown to regulate the host miRNAs repertoire, henceforth, controlling the viral proliferation and dissemination [88]. Moreover, several studies hypothesized that miRNAs that were activated by the coronavirus could regulate the host’s antiviral immune responses including viral sensing [98], cytokine secretion [93,99], and T-cell mediated cell killing. For instance, nucleocapsid protein of the coronavirus OC43 attaches to miR-9 and turn on Nuclear Factors light-chain- enhancer of B-cells (NF-eB), which is a prototypical proinflammatory signalling pathway that has been associated with several chronic diseases and viral illnesses when its expression is dysregulated by the invading virus [100]. Although host miRNAs could be either regulated or utilized by the invading virus. Viral miRNAs are also players in this host-pathogen interaction in which they modulate the expression of the host gene, stress genes, proliferation of cells, and expression of the virus genes [101].

Khan et al. hypothesized that genomic differences between the SARS-CoV-2 virus isolates could have contributed to variation in binding to host miRNAs and hence differences in the virus pathogenicity, symptoms and signs of the disease and the incubation period. On the contrary, viral miRNAs could differ in their effect on regulating the expression of the host gene that could be advantageous or disadvantageous to the virus or the host [102]. Given the rapid mutation rate of the virus genome in the SARS-CoV-2 samples in various global places, it is now accepted that this could have played an important role in determining the severity of the illness and mortality rate among patients infected with SARS-CoV-2.

Human miRNAs targeting SARS-CoV-2

Khan et al., identified in their experiment 106 host anti-SARS-CoV-2 miRNAs and only three (has-miR-17-5p, has-miR-20b-5p, hsa-miR323a-5p) host miRNAs against SARS-CoV-2 were found to have an antiviral effect during host infection [102]. Ace2 mRNA and Ace2 protein levels were inhibited by miR-20c in rat primary cardiomyocytes and in human iPSC-derived cardiomyocytes, thus miRNAs could reduce SARS-CoV-2 infection (as ACE2 serves as the entry gate for SARS-CoV2) [103]. Host miRNAs could also have a well-established role in preventing the viral invasion of the host system through blocking target pathways needed for viral penetration and other significant pathways for viral replication and diffusion. For instance, blocking some molecules such as - p38 MAPK signalling [104], FAK signalling pathway [105], p13K-Akt signalling pathway [106] that could be controlled by the virus for effective pre-miRNA processing and replication. Additionally, these host miRNAs can alter some of the host inflammatory responses to inhibit collateral damage to susceptible organs such as the lungs, therefore, protecting the lung from possible lung injury by targeting IFG1 signalling, VEGF signalling, PAR1 signalling, integrin signalling, and TGF-beta signalling [102]. Interestingly, there is evidence that apart from protective roles of miRNAs, some of the host miRs play an active role in the viral infection through downregulating some of the pathways intended to illicit an efficient immune response, thus supporting viral survival in infected cells by preventing early immune responses such as viral apoptosis and autophagy, thus could inhibit host immune surveillance pathways and function as a pro-viral factor. Recently, it was found that some viral miRNAs can also regulate host gene expression by mimicking cellular miRNAs or engaging in novel modulatory relationships, thus, taking advantage of predefined host regulatory pathways and therefore affecting viral replication and pathogenesis [53]. Despite that the main action initiated by host miRNAs is to inhibit the viral RNA, however, miRNAs role can be described as a double-edged sword that eases viral invasion of the host immune system by interfering with some critical immune pathways [107]. This is strikingly exemplified by the fact that host miRs can facilitate viral replication dissemination in the system, furthermore, they can suppress the expression of host miRNAs that function as a represor of viral replication. Consistent with these data, Khan et al., highlighted several important pathways within the host immune system like- IFN-gamma signalling, TGF-beta signalling, Interleukin signalling, IFG1 signalling, TRAIL signalling pathways, that are associated with several important proinflammatory pathways that signal the release of the cytokine during viral infection [102]. Surprisingly, the authors have also documented host miRNAs are also triggered when infected with SARS-CoV-2 and may specifically suppress various Toll-Like Receptors (TLR) signalling pathways which are regarded as essential stimulatory molecules for producing host anti-viral defense system like the induction of inflammatory cytokines and other interferons. Notably, host miRNAs can also impede several receptors that are involved in signalling anti-viral responses such as uPA-uPAR signalling, TRAF6 signalling, STIP1 signalling, Estrogen receptor signalling, Protease-activated Receptor (PAR) signalling, and bone morphogenetic protein (BMP) signalling pathways, resulting in downregulation of the host anti-viral defense mechanism [102].

Nucleic acid-based therapeutics for inhibition of miRNAs function

The biological process of RNA interference (RNAi) which are defined as small complementary RNA duplexes that neutralize and interfere with certain mRNA molecules, resulting in silencing of gene translation and gene expression. There are two distinct types of RNAi molecules: small hairpin RNA as shRNA, which are synthetic RNA molecules that are synthesized in vitro with a tight hairpin turn that can be used to inhibit their target sequences, hence serves as a precursor of siRNAs [108]. It is crucial to know that the shRNAs expression inside the cells can be achieved through their delivery via commercially available reagents in vitro such as bacterial or viral vectors, or plasmids [109]. miRNA is noncoding and naturally found in viruses, animal species and plants, synthetic miRNAs are developed recently to silence or restore the function of a variety of genes [110].

In contrast to miRNAs and siRNA, the antisense transcript RNA is single-stranded RNA with a sequence complementary to the messenger RNA (mRNA) rendering it the ability to hybridize and hinder protein translation. Anti-sense RNAs are either natural or synthesized, they are generally about 19–13 nucleotides [109]. Developing antisense inhibitors can be used as a restorative technique by inhibiting the overexpression of mature miRNAs sequence that is involved specifically in disease pathogenesis. With the new advancement in medical technology, it is becoming possible to artificially synthesize adjusted analogue of miRNAs as well as siRNAs that can modulate disease-related gene expression and or even block gene expression of the pathogen. Providing exogenous miRNAs can help restore the normal cell function by resetting miRNA expression [108]. Presently, mature miRNAs can be down-regulated by experimentally upregulating the expression of the sites where they bind (miRs “ sponges”) or through giving the anti-sense oligonucleotides (ASO) using pharmacological approaches [111]. One of the advantages of using miRNA inhibitors is the predictable specificity of pairing the inhibitor to their target miRNA using Watson-Crick base pairing. This is an important advantage over e.g. small molecules which have unpredicted specificity to their target. As a result, designing a target for miRNAs with drugs that have nucleic acid structure presents an optimistic therapeutic
option to change the medicinal chemistry perspective of drug development, and therefore cutting down cost and time. As an example, the treatment of AntimiR-155 in a miR-155 “addicted” lymphoma case was efficient and had a higher precision to target the diseased cells compared to the current treatment [112]. Scientists found that several chemical modifications can enhance the binding of nucleotide-based miRNAs inhibitors to their target miRNAs, their stability against nucleases could reduce the cell’s negative charge which inhibits penetration [113]. Nucleic acid-based inhibitors are referred to as anti-miRNAs. Despite that miRNAs inhibitions can be in vivo, however, the most challenging aspect of inhibiting miRNAs in vivo is the delivery of anti-miRNAs to the target gene. To overcome this challenge, miRNAs are conjugated to artificial carriers or are packaged into various delivery vehicles [31,32,113–115]. Artificial carriers can enhance cells uptake in vivo beside it increases the efficacy and precision for target cells and organs [116–118].

Short locked nucleic acid (LNA)- which are modified ASOs that can target miRNAs seed region, present another promising class of anti-miRNAs [119]. The LNA seed family inhibitors can block entire miRNA families and not only individual-specific miRNAs. Interestingly their bioavailability in vivo is optimal without the need for special carriers which makes them a promising class of anti-miRNAs. In a recent study, LNA- modified anti-miR-21 could suppress lupus disease in animals and psoriasis in patients with derived skin xenotransplants [120,121]. These are promising results as mice with a miR-21 deficiency do not exhibit any detectable defects proposing that there will be few to no adverse effects to inhibiting miR-21. Moreover, anti-miR-21 absorption by the skin has dramatically affected the disease outcome. This suggests that topical modes of drug delivery of anti-miRNAs readily can access the body surface (skin, eyes, oral cavity, airways, rectum and vagina) and presents an ideal substitution to overcome the challenges of systematic administration in vivo [121].

**Therapeutically enhancing miRNAs expression**

In contrast to the aforementioned therapeutic options, it might be intuitive to pharmacologically affect miRNAs role, either to replace lost miRNA function or to downregulate an overexpressed miRNA pathway, depending on the clinical scenario. For instance, when inducing miR-146a, it is anticipated to have suppression of certain immune pathways since it will negatively regulate various immune cells and enhance regulatory T cells role [35]. Alternatively, miR-210 which is activated in hypoxic conditions negatively regulates the TGF-β driven differentiation. Therefore, downregulation of TGF-β driven inflammation can be achieved by delivering miR-210 mimics [122]. Another attractive option is the induction of transcription of endogenous miRNAs instead of delivering miRNA mimics. Achieving this could be done by using CRISPR-based approaches [123]. Furthermore, targeting RNA structure or miRNAs processing is another interesting approach that has been exploring relatively. The presence of extensive miRNA secondary structures and multi-step maturation offer excellent venues for pharmacological interventions. Therefore, several strategies could be utilized to enhance miRNAs function. As an example, using a modified oligoribonucleotide termed “looptomer” to target the pre-let-7a-2 was a very successful approach [124]. Table 2. Present a summary of the development status of miRNAs based therapeutics.

**miRNAs as biomarkers in COVID-19**

In addition to the search for the treatment of COVID-19, the search for non-invasive COVID-19 biomarkers for diagnosis is also an urgent need, and this area of research is currently under extensive investigation and considered a rapidly growing area of research [127]. Since miRNAs have been approved to have a key role in the pathogenesis of different respiratory viral infections and to regulate host-pathogen interactions, therefore, miRNAs could serve as a potential prognostic indicator or biomarkers for respiratory virus diseases including SARS-CoV-2. In this section, we present a brief and updated review on the most updated findings in relations to the use of miRNAs overexpression and/or under-expression during different respiratory viral infections to serve as biomarkers.

Recently, several reports indicated increased or decreased amount miRNAs in circulating as a response to pathogens, this increased the potential to be as a novel tool for diagnosis [128]. Using miRNAs as diagnostic biomarkers have brought some advantages for assessment of immune-related diseases, viral infections, and cancer. These small RNAs do not only exist inside cells or tissues but also, they exist in the circulating plasma. The first miRNA was found inside the plasma was miR-21 [129,130]. Later, another study detected about 91 out of 101 miRNAs exist inside the plasma, such as Let-7, miR-25, miR-192, miR-221 and miR-451 [131]. They exist either in micro-sized vesicles or bound to other content in the plasma to teleport from one tissue to another. This helps in remote communications between one tissue and another. Moreover, miRNAs expression is tissue and temporal specific [129]. The expression of miRNAs changes with the cause of the illness, as in one study, it was found that miRNAs which were highly expressed in non-small cancer lung cell were different from those expressed in colorectal cancer and type 2 diabetes [131]. Also, levels of some miRNAs were changed during some viral infections, and those miRNAs were specific to the virus which causes the infection. For example, a study found that miRNAs expressed during varicella-zoster viral infection were different from those expressed during enteroviral infection [131], miRNAs can also help in distinguishing between active and latent infection. Expression of miRNAs was different between active TB, latent TB, and healthy individuals, meaning that it is possible to detect which stage of illness based on miRNA expression [128].

Therefore, several reports showed that miRNAs have promising potentials as diagnostic biomarkers for COVID-19 due to the following advantages; they can differentiate between an infection caused by SARS-CoV-2 from other infections that have the same manifestation like influenza, rhinoviruses or other coronaviruses. Nonetheless, miRNAs can distinguish the possibility of bad vs good disease outcomes, which have great significance in epidemic or pandemic diseases [128]. A study has found that about 34 miRNAs of positive-sense viral RNA and 45 of negative-sense viral RNA interact with specific important SARS-CoV-2 genes. It can be used to monitor different stages of the disease, assess prognosis, plan for treatment strategy, and to measure the outcome of the planned therapy. Moreover, altered expression of miRNAs can affect the levels of cytokines and chemokines, which are responsible to cause the “cytokine storm” during the SARS-CoV-2 infection. This concludes that changes in miRNA expression can help in diagnosis and prediction of the severity of the COVID-19 infection [132].

**Promises of miRNAs as the future of medical intervention**

miRNAs are unique and fulfill several criteria that define good drug options, making them an attractive therapeutic target [133]. Despite their role in modulating individual target genes, the coevolution of miRNAs and their targets resulted in the modulation of an entire immune pathway. Although only recently we begin to understand little information of the full spectrum for the role of miRNAs, their involvement in the control and pathogenesis of the disease has established wide interest for their usage in the regula-
tion of the immune pathways, presenting an optimistic therapeutic option for several emerging disease [134]. For a miRNA to be considered as an optimal drug target, it needs to have an expression that is specific for certain tissue. A good example will be the miR-122 that have specific expression inside hepatocyte therefore, miR-122 inhibitor will only show effects in hepatocyte [135]. Biologists believe that several different miRNAs are expressed when there is an active disease in the host system. Notably, the unusual upregulation of this specific miRNA in numerous other diseases may be pathogenic and have the expression in certain tissues only. For example, miR-122 has a high level of specific expression in the hepatocyte, therefore, blocking miR-122 will only show action in the liver. Biologists believe that a certain number of miRNAs are upregulated in association with certain diseases or infections. Notably, the expression of these specific miRNAs in certain infectious states makes it critical to identify disease biomarkers and develop novel techniques to target viral infections like COVID-19 for diagnosis and treatment.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Declaration of Competing Interest

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.

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Table 2

| Company               | Targeted miRNA | Disease                           | Mechanism | Clinical Trial Status   |
|-----------------------|----------------|-----------------------------------|-----------|------------------------|
| Regulus Therapeutics  | miR-122        | Hepatitis C                       | Anti-miR  | Preclinical             |
|                       | r-10b          | Globlastoma                       | Anti-miR  | Preclinical             |
|                       | miR-221        | HCC                               | Anti-miR  | Preclinical             |
|                       | miR-21         | Renal fibrosis                    | Anti-miR  | Preclinical             |
|                       | miR-33         | Atherosclerosis                   | Anti-miR  | Completed preclinical   |
|                       | miR-17         | Autosomal dominant polycystic kidney disease | Anti-miR | Preclinical           |
|                       | miR-27         | Cholestatic disease               | Anti-miR  | Discontinued            |
| Santaris Plasma       | miR-122        | Hepatitis C                       | Anti-miR  | Phase-II               |
| Mirna therapeutics    | miR-34         | Primary liver cancer              | Mimic     | Phase-1                |
|                       | miR-155        | Hematological malignancies        | Anti-miR  | Completed preclinical   |
|                       | miR-215        | Cancer                            | Mimic     | Preclinical             |
|                       | miR-101        | Cancer                            | Mimic     | Preclinical             |
|                       | miR-16         | Cancer                            | Mimic     | In pipeline             |
|                       | let-7          | Cancer                            | Mimic     | In pipeline             |
| miRagen therapeutics  | miR-92         | Peripheral artery disease         | Anti-miR  | Preclinical             |
|                       | miR-15/195     | Myocardial infarction             | Anti-miR  | Preclinical             |
|                       | miR-155        | Cutaneous T-cell lymphomas        | Inhibition | Phase-I                |
|                       | miR-208        | Chronic heart failure             | Inhibition | In pipeline             |
|                       | miR-143/145    | Vascular disease                  | Inhibition | In pipeline             |
|                       | miR-29         | Cardiac fibrosis                  | Inhibition | In pipeline             |
|                       | miR-451        | Abnormal red blood cell production | Anti-miR  | Discovered              |
|                       | miR-92         | Peripheral arterial disease       | Inhibition | In pipeline             |

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[118] Dr. Tareq Abu-Izneid is an associate professor in pharmaceutical chemistry at the college of pharmacy, Al Ain University, United Arab Emirates. Dr. Tareq received his PhD. from the Institute for Glycomics, Griffith University, Qld, Australia, in 2005. His research interest is in pharmaceutical sciences in general, and his current focus is on studying and designing anticancer and antiviral drugs (from synthesis and natural sources). To date, he has authored many publications in various peer-reviewed journals.

[119] Dr. Noora Alhajri is a Clinician-Scientist who received her training in the United States of America and Ireland. She earned her Doctor of Medicine (M.D.) degree from the prestigious Royal College of Surgeons of Ireland (RCSI) with first class honours (H1:1). Following her graduation, she got accepted at George Washington University where she accomplished her Master of Public Health Degree (MPH) with a GPA (4.0/4.0). During her MPH training she got accepted at the World Health Organization (WHO) where she worked with a team of international leaders and developed a tool to promote the Social Accountability of Medical Education (I-SAT). She then received a grant from the National Institute of Health (NIH) in Baltimore, Maryland, to pursue her post-doctoral fellowship training at the prestigious Johns Hopkins University (JHU) division of Vascular Surgery, and Endocrinology, Diabetes, and Metabolism. Dr. Alhajri also worked as a visiting scientist at the Division of Cardiovascular Science at the NIH. During her Post-Doc fellowship training she published several scientific papers in international peer-reviewed journals. Dr. Alhajri was recently accepted as a fellow in training at the American Heart Association (AHA) as well. In addition to her main research interest in peripheral artery disease in women, she is interested in revascularization and endovascular interventions for peripheral artery disease in men.

[120] Mr. Abdallah Mohammad Sudqi is serving as a Lecturer in the nursing college, Imam Abdulrahman Bin Fahd University, Saudi Arabia. He holds master degree in pharmacology from university of Jordan since 2010. Interested in neuroscience, oncology, virology and genetics. To date, he has authored many publications in various peer-reviewed journals.

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Dr. Md. Noushad Javed is currently working in lab of Professor M. Zahid Ashraf at Jamia Millia Islamia on neuroprotective potential of TLR agonist. He has completed PhD in Pharmacy at School of Pharmaceutical Education and Research, Jamia Hamdard University, New Delhi, India (Rank #1 in Pharmacy institute as per Govt. of India). In past, he has associated with various academic and research positions which includes: Appejay Stya University; Dibrugarh University as well as consulted independent industrial assignments. He is a registered clinical pharmacist and herbalist by professional training. While, he is also a certified statistical analyst as well as an expert of international regulatory affairs and pharmaceutical patents. His interest are towards integration of holistic in-silico based approach such as computational bioinformatics; Quality by Design (QbD) and statistical approaches for validation of analytical methods and processing of novel materials; to be used as site targeted controlled release formulations for various inflammatory disorders. Till date, he has authored more than 40 publications including research and review papers in high impact peer-reviewed journals and some patent applications. Dr. Javed has also been invited for lectures and oral talks at several international conferences. He has also been awarded with various medals and best presentation awards by reputed society. He is also serving as an accredited reviewer and editorial board member of some journals. While recently handled special issue in the journal Current drug metabolism (Bentham Science)

Dr. Faheem Hyder Pottoo is working as an Assistant Professor, Department of Pharmacology, College of Clinical Pharmacy, Imam Abdulrahman Bin Faisal University, Saudi Arabia. He got his M.Pharm (Pharmacology) from the Department of Pharmacology, School of Pharmaceutical Education & Research, Jamia Hamdard, New-Delhi, India and PhD (Pharmacology) in 2016 from Department of Pharm. Sc. Faculty of Applied Sc. and Tech., University of Kashmir, India. His research vision is to transform the treatment of neurodegenerative diseases & cancers by modulating signalling pathways. To date, he has authored more than 75 publications in various peer-reviewed journals. The recent paper being “Targeted Delivery of miRNA Based Therapeuticals in the Clinical Management of Glioblastoma Multiforme https://pubmed.ncbi.nlm.nih.gov/32302695/” in the Journal Seminars in Cancer Biology (IF: 11.09). He has filed many patents and serves as a review editor in the neuropharmacology section for the journals Frontiers in Neuroscience, Frontiers in Neurology & Frontiers in Pharmacology.

Dr. Faheem Hyder Pottoo

Dr. Khairi Mustafa Salem is currently working as a Professor and Dean at the Department of Pharmacy, Al Ain University of Science and Technology, United Arab Emirates. His research interests includes Pharmacy, He is serving as an editorial member and reviewer of several international reputed journals. Dr. Khairi Mustafa Salem is the member of many international affiliations. He has successfully completed his Administrative responsibilities. He has authored of many research articles/books related to Pharmacy.

Dr. Khairi Mustafa Salem

Dr. Mohammad Amjad Kamal is a Distinguished Adjunct Professor at the King Fahd Medical Research Center (KFMBRC), King Abdulaziz University, Saudi Arabia. He is leading a highly productive global collaborative research team based on the Novel Global Community Educational Foundation (NGCEF), Australia. Prof. Kamal’s biochemical research in the field of Alzheimer’s disease, Type 2 diabetes and leukemia has culminated in more than 500 publications in internationally respected journals. He was awarded a prestigious U2000 Postdoctoral Fellowship in 2000 by the University of Sydney. Amongst numerous projects, he also collaborated on the molecular biological research project “Linkage of Alzheimer’s disease and Type 2 diabetes” at the University of Technology, Sydney. Moreover, he is serving as a regional/guest editor of several reputed scientific journals on an honorable basis.

Dr. Mohammad Amjad Kamal

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