International Journal of Progressive Sciences and Technologies (IJPSAT)
ISSN: 2509-0119.

http://ijpsat.ijsht-journals.org
Vol. 30 No. 2 January 2022, pp. 404-415

miRNAs and COVID-19 Therapy Review

Maged Naser[1], Mohamed M. Naser[2], Lamia H. Shehata[3]

[1]Mazahmiya Hospital, Ministry of Health, Kingdom of Saudi Arabia, Department of Obs/Gyn,

[2]King Fahd Hospital, Ministry of Health, Kingdom of Saudi, Department of Surgery, Consultant Endoscopic Surgery,

[3]Department of Radiology Care National Hospital, KSA

Highlights

- **The novel Covid disease 2019 (COVID-19) is caused because of SARS-CoV-2 infection which has been declared a pandemic.**
- **The significance of miRNAs in the pathogenesis of this viral disease is summed up.**
- **Right now, there is no approved treatment or immunization for COVID-19 and miRNAs can come to become a potential therapeutic tool.**
- **This work depicts the idea of developing Nano formulation(s) of the SARS-CoV-2-related miRNAs.**
- **Multi-targeting methods are needed for miRNA Nano-therapy for effectively tackling SARS-CoV-2.**
- **The Nanoparticles-based miRNAs could be utilized in the form of Nano-vaccines for the prevention from SARS-CoV-2.**

Abstract – These days, the extreme intense respiratory condition Coronavirus 2 (SARS-CoV-2) disease is recognised on the grounds that the primary cause behind mortality in people. SARS-CoV-2 is transmitted through human-to-human contact and is a symptomless in many patients. furthermore, to approved vaccines against SARS-CoV-2 infection, miRNAs may additionally be promising decisions against the current new virus. miRNAs are small and noncoding RNAs 18–25 nucleotides in length that focus on the mRNAs to degrade them or block their interpretation miRNAs go about as an observer in cells.

This review in regards to evaluated the writing on the potential role of cellular miRNAs inside the SARS-CoV-2-have collaboration as a therapeutic option in COVID-19 patients.

Keywords – Coronavirus, COVID-19, miRNA, SARS-CoV-2.

I. INTRODUCTION

A novel Coronavirus disease2019 (COVID-19) has a place with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and has been set in humans for the first time [1]. Covid has been joined to a classification of pathogens that impacts the respiratory system of humans. According to World Health Organization (WHO), COVID-19 has symptoms beginning from common cold to high fever, and difficulty in breathing. In severe infection conditions, COVID-19 can be an acute respiratory syndrome that ends in nephrosis, and advances to death [2–4]. Before SARS-CoV-2, 2 fundamental remarkable Covids, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East respiratory Syndrome Coronavirus (MERS-CoV) are set [5]. Coronavirus has been brief to rise up out of Wuhan, Hubei, China, at the end of December 2019 when few of patients were

Corresponding Author: Maged Naser

admitted to the emergency clinics known with unexplained respiratory disease and later this spread be suspected to be connected with the wet market in Wuhan, China [6,7].

The SARS-CoV-2 has a place with the β-subfamily of Covids very much like SARS-C0V and MERS-COV [8,9]. Among all totally unique seven types of Covids, β-subtype is that the most deadly [8]. Covids were introductory known through Tyrell and Bynoe in 1966 as positive single stranded, encased ribonucleic acid virus with a genomic size of 26–32 K, which will infect both mammals and humans [10]. Through writing, it's been contemplated that SARS-CoV-2 comprises of four underlying proteins (the spike, film, envelope, and nucleocapsid) and ribonucleic acid and RNA viral genome. the entire construction is with respect to 60–140 nm in diameter. The construction of SARS-CoV-2 is considered to be a core-shell morphology.

Covids conjointly replicate inside the host living substance, as various ribonucleic acid viruses [11]. As of late, mean reports advised that SARS-CoV-2 was toward the start sent from bats [12,13] and furthermore the whole genome of human SARS-CoV-2 was found out to be almost 96 same to the Covid of a bat [9]. Bats had been acclaimed in light of the fact that the natural reservoir for different Covids, similar to SARS-CoV, MERS-CoV, HCoV-NL63, and HCoV-229E [14–16].

Most COVID-19 patients had been accounted for to have another hidden comorbidity factors, as diabetes, respiratory infection, cardiovascular condition, hypertension, and cancer [3]. predictable with a many reports, the median age of COVID-19 legitimate cases/patients was around sixty years and older, and over a large portion of the population were males. The average incubation time for the infection is ~5 days [3,17].

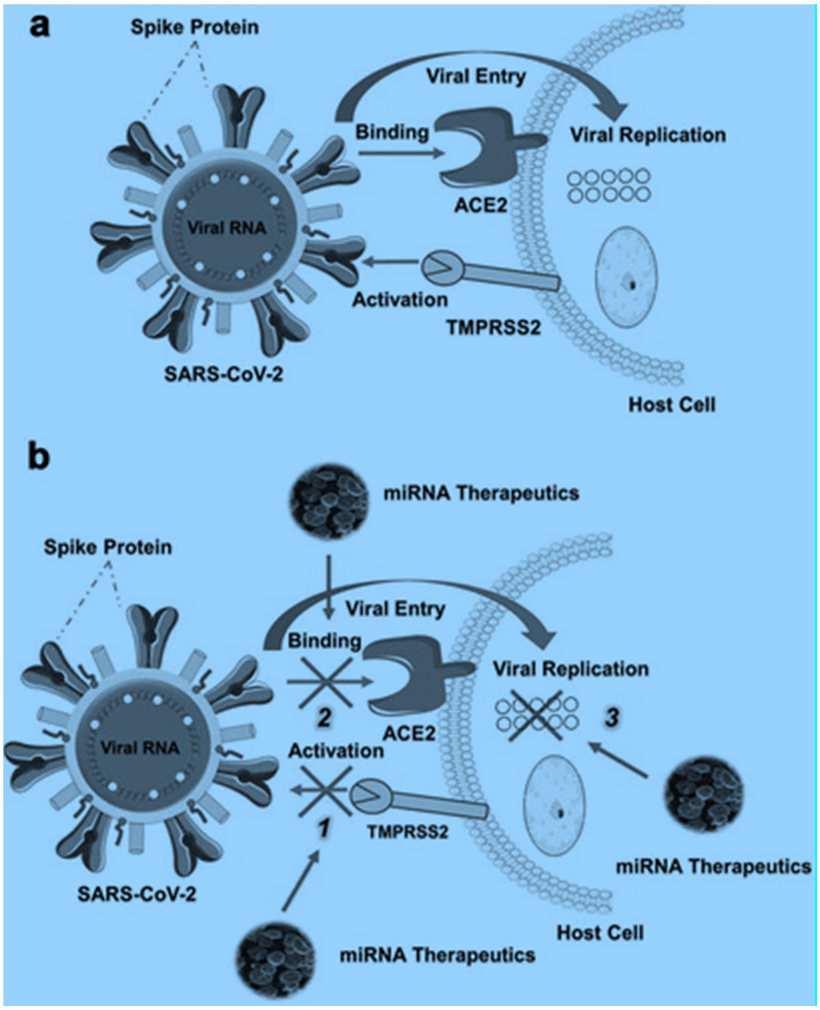

Figure 1

The most ideal course ascribing to the transmission of this SARS-CoV-2 virus spread is human to human contact [18,19] (Figure 1(a)). Upon the transmission, virus particles bind to the host cell receptor then, at that point, get fused with the cell

membrane. Being a disease, principally, SARS-CoV-2 was once obvious to target the air way and lung epithelial tissue cells. Developing confirmations contend that receptor binding domain of SARS-CoV-2 spike macromolecule gets enacted when its cleavage by Transmembrane amino acid proteinase two (TMPRSS2) and binds to the Angiotensin-Converting enzyme 2 (ACE2) receptor of the host cells (Figure 1(a)) [20–22]. Thusly, we tend to guess that recognizable proof and useful conveyance of microRNAs that involved in impeding the limiting or actuation with ACE2 or TMPRSS2 is particularly fulfilling for the prevention and the management of COVID-19 (Figure 1(b)).

II. Relationship with SARS-CoV and MERS-CoV

Coronavirus has many similarities with the previous 2 viral infections of its family.

SARS-CoV and SARS-CoV-2 infections have started in China and been linked together with animal markets. Coronavirus and MERS both mentioned to be symptomless in a really large number of cases [23]. nonetheless, COVID-19 has conjointly been recorded as a contagious and respiratory disease that is one more closeness with SARS and MERS [4]. Transmission of all the 3 worldwide health threats has conjointly been by similar means as human to human contacts and, through cough and sneeze droplets in the air [24,25].

Additionally, the receptor-binding domain sequence of SARS-CoV-2 is similar to that of SARS-CoV [11]. SARS acclimated to be a world epidemic exploded in 2003 [26] while MERS acclimated to be the second Covid pandemic and was once introductory announced in 2012 in Saudi Arabia [26]. Reports claimed that these infections have risen up out of bats and camels and communicated to humans [27,28]. The spread of both viral infections (SARS and MERS) was worldwide as early clinical features had been at this point not clear. MERS acclimated be less severe in differentiation to SARS condition since it did don't really show world transmission rapidly, not in any event, when 2 years of its underlying rise. Past measures taken to battle SARS and MERS became reconsidered to better handle this extra newer world pandemic, including, maintaining social distancing, proper hygiene, self-quarantine (assuming any manifestations are present), and isolation (of affirmed positive individuals) [4].

III. miRNAs in SARS, MERS and COVID-19 viral disease

microRNAs (miRNAs) region unit in regards to 18–25 nucleotides in length, small non-coding RNAs that change the objective mRNAs post-transcriptionally, accordingly, watch guard dogs inside the cells [29,30]. inside the past most recent years, several surveys have perceived miRNAs as signature biomarkers that assume a significant part in various cellular processes, as cellular proliferation, apoptosis, differentiation, and embryonic development [31]. Dysregulation in the expression status of miRNAs has been connected with changed diseases comprising of viral diseases, tumours [31,32], diabetes, schizophrenia [33,34], psoriasis [35], and cardiovascular diseases [36].

Growing evidences have proposed a fundamental role of miRNAs inside the pathogenesis and therapeutics of the numerous viral diseases (Table 1), like dandy fever, Influenza, Human immune deffiency Virus one (HIV-1), Herpes Simplex Viruses (HSV), and hepatitis C (HCV). A review has previously mentioned that miRNA 122 has strong anti- HCV characteristics [37]. Based on a bioinformatics study, a group13 cellular human miRNAs regulate the MERS-CoV. Out of those, exclusively 3 human miRNAs, miRNA 628–5p, miRNA 18a-3p, and miRNA 332–3p have the known biological functions. Staying 10 human miRNAs (miRNA 6804–3p, miRNA 4289, miRNA 208a-3p, miRNA 510–3p, miRNA 329–3p, miRNA 548ax, miRNA 3934–5p, miRNA 4474–5p, miRNA 7974, and miRNA 6865–5p) don't really play any role/functions in humans or animals. miRNA 628 and miRNA 332 showed remarkable identity with the MERS-CoV viral genome. As of the previously, miRNA 628 has been referenced to play growth suppressive situation in glioblastoma any place it's vital for cell multiplication and cell cycle progression [38]. miRNA 18a was also found to extensively change the genes associated with cellular proliferation, adhesion, and differentiation [39]. On the other hand, miRNA 332 acclimated be supported to be overexpressed in prion disease and critical for late phase of the disease [40]. Considering the similarity among MERS and COVID-19, these miRNAs need to try and be likely potential for COVID-19 clinical therapeutics.

Table 1. Role of different miRNAs in viral diseases

Virus	miRNA	Function
James Canyon Virus (JCV)	miRNA J1 (Viral)	Downregulates early gene expression{41)
Human Papillomavirus (HPV)	miRNA 203 (Cellular)	Downregulates expression of p63(42)
SARS	miRNA 17 and miRNA 214 (Cellular)	Facilitates gene replication and helps in immune Invasion(67)
Herpes Simplex Virus (HSV)	miRNA LAT (Viral)	Anti-apoptotic role(43)
Hepatitis C Virus (HCV)	miRNA 122 (Cellular)	Enhances viral replication(44)
Human Immunodeficiency Virus (HIV)	miRNA N367 (Viral)	Reduces LTR transcription(45)
Human Cytomegalovirus (HCMV)	miRNA UL23 (Viral)	Immunomodulation(46)
Simian Virus 40 (SV 40)	miRNA S1 (Viral)	Downregulates early gene expression(47)
Influenza	miRNA 507 (Cellular)	Helps adapting influenza AI (Avian Influenza) to mammalian cells/species via targeting PB2mammalian cells/species via targeting PB2 (66)
BK Virus (BKV)	miRNA B1 (Viral)	Downregulates early gene expression(48)

Additionally, many studies have been performed with SARS including its relationship with miRNAs. Qin et al. have used miRNA (Small non-coding RNA) based therapy to reduce the spike gene of SARS-CoV [49]. This methodology can likewise be used for SARS-CoV-2 inhibition as the spike protein of this virus is concerned in the binding and fusion to the host cells.

Studies even guided that some plant miRNAs are furthermore identical with human miRNAs as they share equivalent genomic sequences [50]. One plant-based miRNA, pab-miRNA 11409d found in gymnosperm Picea abies (L), affirmed sequences likeness with 3′ of SARS-CoV-2 spike gene (NCBI Accession assortment LC528233.1), recommending that it might also be used to cure the COVID-19 [51]. Anti-viral miRNAs present in the host cells are likewise of extraordinary importance as they go about as a basic controller of immune response by focused on viral gene replication and expression all through the viral infections. A geological (USA, Wuhan, Italy, India, and Nepal) genomic study into on COVID-19 showed six anti- viral host cell miRNAs specific to SARS-CoV-2, for example, hsa-let 7a (targets Non Structural Protein), hsa-miRNA 101 (targets Non Structural Protein), hsa-miRNA 126 (targets Nucleocapsid), hsa-miRNA 23b (targets spike protein), hsa-miRNA 378 (targets nucleocapsid), and hsa-miRNA 98 (targets spike protein) [52].

Patients suffering with diabetic and heart diseases who are on ACE2 enhancement drugs (inhibitors and blockers that make greater the expression of ACE2 receptor), are extra inclined to be infected with SARS-CoV-2 [53], and ACE2 was seen to be controlled via hsa-miRNA 27b [52,54], hence, these discoveries likewise inform of a significant relationship between hsa-miRNA 27b and SARS-CoV-2. It is likewise fundamental for notice that miRNA 27b is related with Indian starting variation genome of SARS-CoV-2 [52]. Viral protein replication/synthesis happens in the host cell and miRNAs hinder the interpretation of target mRNA into the protein; thusly, miRNAs can be used as a therapeutic tool for viral diseases [55–57].

Considering the importance of miRNAs, it transforms into imperative to identify the miRNAs directing the pathogenesis of COVID-19 and/ or other corona diseases. One more way to deal with control COVID-19 or potentially unique two Covid afflictions is, to utilize completely complementary miRNAs (cc miRNA) that can focus on the viral gene and hinder its post-transcriptional expression. The cc miRNAs (altered to 25–27 nucleotides), namely, ID02510.3p-miRNA, ID00448.3p-miRNA, miRNA 315 4, miRNA 7114–5p, miRNA 5197–3p, ID02750.3p-miRNA, and ID01851.5p-miRNA showed a solid restricting with the SARS-CoV-2 viral genome, suggestively [58].

The izMiR (miRNA prediction software) and PANTHER, bioinformatics essentially based grouping frameworks, perceived the possible mature viral and host cell miRNA candidates that should play an essential role in SARS-CoV-2 infection [59]. As indicated by this review, SARS-CoV-2 genes (Spike, Envelope, Membrane, Nucleocapsid, ORF1ab, ORF3a, ORF6, ORF8, ORF7a, and ORF10) had been targeted through different human miRNAs (Figure 2) and these miRNAs as of now play ahead of time recognized parts in numerous viral diseases, to delineate, ORF1ab and ORF3a, two SARS-CoV-2 viral genes, had been shown to be engaged via hsa-miRNA 203b-3p which was once said to supress viral replication in Influenza [60].

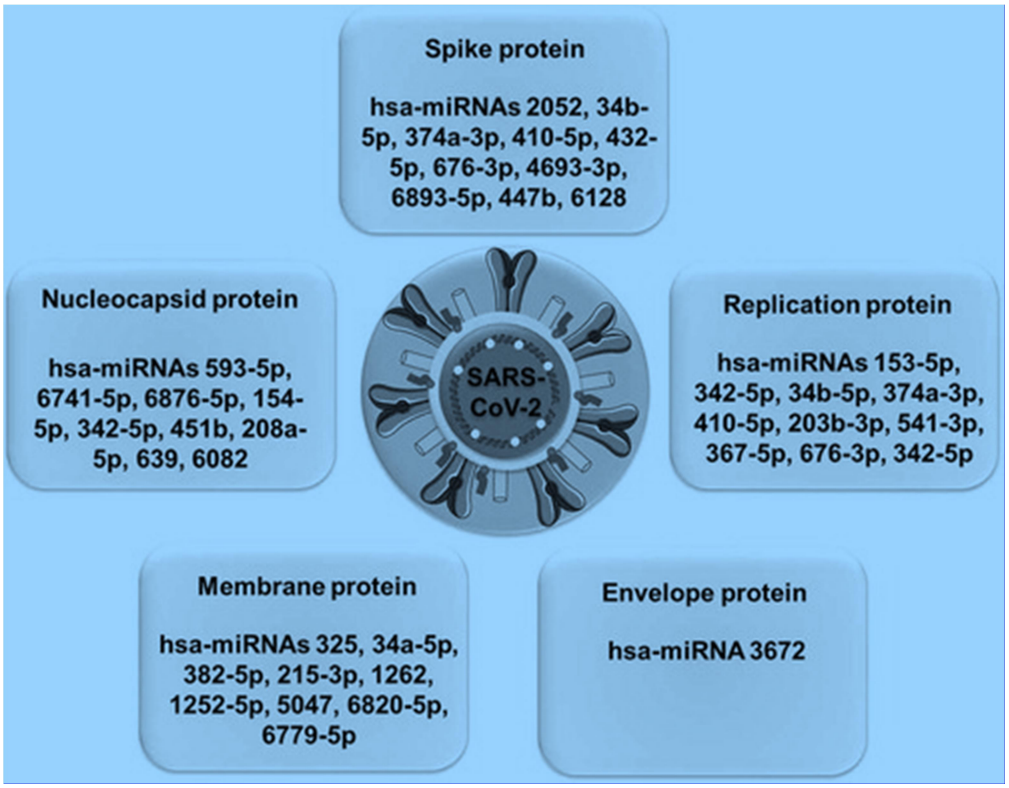

Figure 2. A comprehensive list of host cell miRNAs that target different SARS-CoV-2 proteins

As per a bioinformatics based review, the spike protein of the virus was shown to be targeted by 67 different human miRNAs while this computational prediction demonstrated that ORF1ab gene used to be targeted through 369 miRNAs [59]. Then again, 18 SARS-CoV-2 viral miRNAs were furthermore recognized in this study with their practical host cell target genes. Larger part of these target genes were transcription factors and mediators of RNA polymerase II, essentially TAF 4, TAF 5, TAF 7 L, SOX 11, TCF 4, TFDP 2, TRPS 1, BRF 1, and MED 1, MED 9, MED 12 L, MED 19, respectively. Some signal transducers, for example, STAT 1 and STAT 5B were likewise announced among the anticipated target genes of viral miRNAs.CHAC1 and RAD9A are

two crucial proteins for apoptosis [61] and found to be targeted by two SARS-CoV-2 viral miRNAs, in particular as miRNA MD2-5p and miRNA 147–3p [62]. Moreover, miRNA 66–3p used to be recognized to target the transcription enhancer of TNF-α, a very well-known cytokine [62]. TMPRSS2 has been connected to activate the spike protein of SARS-CoV-2, accordingly, promotes the disease [22]. This activator gene had been predicted to be targeted by miRNA 147–3p in the gut. This study into likewise distinguished two more viral miRNAs as miRNA 198–3p and miRNA 359–5p that target and enhance the activity of Adenosine Deaminases Acting on RNA (ADAR) and non-muscle myosin weighty chain 9 (MYH9), respectively [62].

IV. miRNAs anti-COVID-19

There are interesting strategies against the SARS-CoV-2 disease: repressing the viral replication, blocking cell receptors and impeding the function of viral proteins. miRNAs can repress 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 influencing the expression of human genes.

For example, ID02510.3p-miRNA, ID00448.3pmiRNA, miRNA 3154, miRNA 7114-5p, miRNA 5197-3p, ID02750.3p-miRNA and ID01851.5p-miRNA, miR-5197-3p [64,65], miR-17-5p and miR-20b-5p [66] mitigate the pathogenesis of COVID-19 disease through restricting to the SARS-CoV-2 genome and hinder its post-transcriptional expression. Nersisyan et al., introduced six miRNAs including miR-21-3p, miR-195-5p, miR-16-5p, miR-3065-5p, miR-424-5p and miR-421 that potentially regulated all human Covids by means of direct binding to the viral genome. The miR-21-3p had the wonderful restricting to the human Covid genome [67].

Balmeh et al., downloaded the nucleotide sequences of 1872 miRNAs beside the miRBase facts base. 42 miRNAs had the very best score, amongst to them miR-1307-3p including the good score showed high affinity to SARS-CoV-2 genome 3′-UTR then had been expressed at a high level in rating in comparison to other miRNAs within lung tissue. Without a doubt, increased expression regarding miR-1307-3p prompts a markdown of SARS-CoV-2 reproduction [63]. Likewise, Chen et al., reported so much mutations in SARS-CoV-2 3′-UTR lead to virus get away from the host immune system [68]. On the other hand, miR-1307-3p do influence anti- apoptotic proteins like BCL2 to induce apoptosis and inhibit proliferation. Likewise, such be able repress the PI3K pathway in accordance prevent cell cycle proliferation [63]. Also, miR-1307-3p involves TGF-β signalling, inflammatory reaction, oxygen dependence, persistent wheezing and chronic lung diseases [69].

Considering so much the structural and non-structural proteins are targeted via human miRNAs, Demirci et al., predicted the viral mRNA targets through cellular miRNAs. These proteins are responsible for viral biogenesis, entry, copy and infection. They found that except for E or ORF6 areas, other viral genes are targeted by multiple cellular miRNAs. For instance, miR-203b-3p, in addition to suppression of influenza virus replication, can target ORF1ab and ORF3a SARS-CoV-2. Likewise, let-7c-5p can target the ORF1ab SARS-CoV-2 and the M1 protein in H1N1 influenza A in accordance with hinder its replication. On the other hand, miR-190a-5p target ORF6 in SARS-CoV-2 and overcome immune system. Thusly, it miRNAs do remain regarded as like an innate antiviral defence system in view as SARS-CoV-2 replicates to inhibit the immune system by decreasing the cellular miRNAs. Additionally, Demirci et al. referenced that miR-148a-3p targets ORF8 in SARS-CoV and prevents viral replication and interspecies transmission.

This finding can be another purpose for the higher transmissibility concerning SARS-CoV-2 contrasted with SARS-CoV [70]. Sardar et al., expressed six cellular miRNAs so much target SARS-CoV-2 proteins: let-7a and miRNA 101 (target the non-structural proteins), miRNA 126 and miRNA 378 (target the N region), miRNA 23b (target the S region) [71]. Additionally, Rad SM et al., put in on so miR-29b-3p, miR-338-3p, miR-4661-3p, miR-4761-5p and miR-4793-5p might also act against the S protein of SARS-CoV-2 [72,73]. Arisan et al., expressed up to expectation miR-8066 have to act against the SARS-CoV-2 N gene, which encodes a basic RNA-binding protein that goes as regards as like both structural and non-structural protein. Thus, targeted this gene be able to reduce or block the assembly and production of viral particles [69].

Sardar et al., confirmed as taking into consideration the importance of cellular receptors, mainly ACE2, within SARS-CoV-2 infection, miRNA 27b manages the ACE2 receptor [71]. Chauhan et al., expressed up that miRNA 200b-3p, miRNA 200 c-3p and miRNA 429 could act against ACE2 and moreover let-7c-5p, miRNA 98-5p, let-7 f-5p, let-7a-5p, let-7 g-5p, let-7b-5p, miRNA 4458, let-7e-5p, let-7i-5p, let-7d-5p and miRNA 4500 may regulate the TMPRSS2. Patients with metabolic syndrome, diabetes and cardiac diseases, are prone to SARS-CoV-2 infection due to increased ACE2 receptor expression, so blocking the ACE2 receptor with miRNAs could be useful therapeutic preference to treat COVID-19 [74]. Widiasta et al., reported that miR-18

upregulated the ACE2 expression in nephropathy patients and suppositional up to expectation that miR-18 ought to keep utilized because of ACE2-related diseases [75]. Arora et al., reported that RIG-I/Ddx58 receptors are particularly upregulated in COVID-19 infection. SARS-CoV-2 hijacks the Ddx58 so much is involved with miRNA biogenesis and mRNA splicing to strengthen its replication. Additionally, miR-124-3p do downregulate the Ddx58 through attachment to 3′-UTR of Ddx58. Consequently, overexpression regarding miR-124-3p would degrade the Ddx58 and diminishing the level of replication of the SARS-CoV-2 genome [76]. Strikingly, SARS-CoV-2 do encode miRNAs to construct overexpression of TMPRSS2 [77] and target several immune signals, for example, TLR, IL, TRAF6 signaling and as a result of it affects autophagy, mTOR signalling and IFN-I signalling. Besides, SARS-CoV-2 miRNAs can target genes that are involved into the Ca+2 signaling pathway [66].

SARS-CoV-2 is associated with myocarditis, cardiac arrest and acute heart failure, but that is no clear whether or not it conditions are problems of COVID-19 health problem and triggered by means of SARS-CoV-2. The just substantial component regarding SARS-CoV-2 infection is the increase in mortality among the older and individuals with underlying conditions. Then again, the expression of miRNAs has been reported according to stand conversely related to age. Along this lines, cellular miRNAs without problems binds to the viral genome in young people beings conversely, aged individuals and people with underlying conditions. Fulzele et al. select several cellular miRNAs against the SARS-CoV-2 genome to that amount are downregulated in the elderly and people with underlying medical conditions. For example, miR-133a (cardiovascular hypertrophy), miR-1, miR-208, miR-328, miR-21, miR-212 yet miR-590 (arrhythmia.) [78], miR-15b-5p (coronary artery disease), miR-15a-5p (kidney disease), miR-520c-3p (obesity/diabetes), miR-30e-3p (myocardial injury), miR-23c (hepatocellular carcinoma), miR-30d-5p (non-small cell lung cancer), miR-4684-3p (colorectal cancer) yet miR-518a-5p (gastrointestinal stromal cancers), are downregulated in pathophysiological conditions [79]. It was confirmed that miR-545-3p and miR-519c-3p are related together with COPD and acute exacerbations that often co-occur with respiratory infections [80]. Additionally, Chow et al., observed 128 portable miRNAs be able to target the SARS-CoV-2 genome. However, most of them bear tremendously low or no expression in lung epithelium. Four out of 128 miRNAs, including let-7a-3p, miR-135b-5p, miR-16-2-3p and miR1275, have been downregulated. Two out of 128 miRNAs, such as, miR-155-3p then miR-139-5p were upregulated [81]. Kawasaki disease is associated with COVID-19 disease in children between 5–15 years. Demongeot et al. affirmed so miR-let-7b is the almost upregulated within kawasaki disease. Likewise, miR-129-5p may have the potential against the S and ORF10 areas among SARS-CoV-2 infection [82].

An extensive alternate about cytokines are involved into the development of SARS-CoV-2 infection. Arisan et al., reported that miR-8066 raises the cytokines concerning PRLR, CXCL6, IL6 or IL17. MiR-5197-3p was known to be the most effective therapeutic option due to interplay with the guide RNA of SARS-CoV-2. miR-3934-3p do downregulate TGFBR1 and SMAD3 pathways to that amount are fundamental for lung fibrosis [69]. Due to the fact of vitamin D and B3 deffiency in SARS-CoV-2 disease, miR-3934-3p may keep related with vitamin digestion and absorption. The level of IL-10 as much certain regarding the pro-inflammatory effector cytokines increased in COVID-19. Nepotchatykh et al., reported that hsa-miR-127-3p could regulate the expression of the BCL6 gene and as a consequence inhibit the expression of IL-10. This cytokine has anti-inflammatory properties and plays a central role in limiting host Immune reactions to pathogens [83]

V. FUTURE PROSPECTIVE

miRNAs have arisen as a newer group of components playing a vital role in the pathogenesis of numerous diseases which incorporate viral diseases with clinically relevant therapeutic applications. In this study, we have featured several miRNAs that have been identified for SARS-CoV-2 utilizing bioinformatics studies. These miRNAs are, be that as it may, exposed to furthermore in vitro and in vivo research, yet all things considered award basic insights on their conceivable role in SARS-CoV-2 infection. As miRNAs regulate the expression of target genes (mRNA), changing the expression status of miRNAs by means of overexpressing or knocking them down, can result in preferred therapeutic results. Viral diseases can have dual functionality of miRNAs as there should be viral miRNAs and host cell miRNAs. Host cell miRNAs should either repress the viral genome or enhance the viral genome replication upon the interaction. Regardless of having these advantages of miRNA therapeutics, transport of uncovered miRNAs is often associated with quick degradation and non-specific target impacts which can be overcome by nanotechnology-based approach methodology.

The fundamental considering development of nanoformulations of the SARS-CoV-2-related miRNAs is to convey these miRNAs effectively and safely to the cells to apply their therapeutic effects. This review has proposed multifacets targeting approach for SARS-CoV-2 using miRNA nanotherapy. Activation of SARS-CoV-2 spike protein upon the cleavage by

TMPRSS2 is the first event of viral disease which furthermore drives the cleaved spike protein to get fused with ACE2 membrane receptor of the host cells. Hence, miRNAs that are specific to activation and binding of spike protein are of excellent remedial potential. Like other delivery systems, Identification of suitable miRNA nanoformulations with predetermined loading efficacy, sustained release, and targeting characteristics, is highly warranted. What's more, miRNAs that could inhibit the viral replication in the host cell, ought to furthermore be enveloped in the nanoparticles to supress the viral load. Other than therapeutic purposes, nanoparticles-based miRNAs probably could be utilized like nano-vaccines for the prevention from SARS-CoV-2. Nano-vaccines have various benefits over traditional immunizations as they are specific for infection site and have minimal to no off-target impacts. Moreover, nano-vaccines can be developed as nasal spray/drops. In case of SARS-CoV-2 disease, nasal spray nano-vaccine is more noteworthy modality as it can directly activate the immune reaction in the respiratory tract, for example, nasal passages as well as the lungs which are the primary contraction sites for SARS-CoV-2 viral infection,

This additionally shows the direct and specific delivery of miRNAs in the targeted sites. It is important to develop a unique and multi-disciplinary team of drug and Nano medicine specialists, and basic and clinical researchers, for the effective clinical translation of miRNA nanoformulations. Nonetheless, utilizing currently Nano medicine innovation has additionally revived the interest for effective implementation of miRNA transport for COVID-19. Oral delivery of therapeutics is dependably an easy step toward making the medications [84]. On account of oral delivery of miRNAs, miRNA availability is somewhat difficult due to the nucleic acid degradation in gastric environment. Hence, making formulations that are appropriate and can be used to oral delivery of miRNAs is perceptibly looked for.

VI. Conclusion

World Health Organization has declared the COVID-19, a world pandemic in February 2020, which has caused multiple million affirmed positive cases and more than quarter million deaths worldwide starting at 8 May 2020. Coronavirus has been reported in people for the first time; there for, development of effective treatment plans is an unmet clinical need. Many research groups have been focusing on insight the genomic profile of the infection and utilizing repurposed medications to treat COVID-19. A very few reports, until this point, have reported the miRNAs as therapeutic molecules for this infection. miRNAs control the post-transcriptional expression of target mRNA genes, in this way, have been reported to play an important role in the pathogenesis of numerous viral diseases which incorporates SARS-CoV and MERS-CoV diseases. In this study, we have shed the light on a various important and prior revealed miRNA in Covid infections and, furthermore how they can be fitting for combating this invisible enemy to safeguard humanity. This ought to be a functioning area for future research to conduct in vitro and in vivo experimental procedures for the clinical translation of miRNAs into COVID-19 therapeutics.

Conflict Of Interest

All authors declare no conflicts of interest.

Authors Contribution

Authors have equally participated and shared every item of the work.

References

[1]- Chang, Le, Ying Yan, and Lunan Wang. "Coronavirus disease 2019: coronaviruses and blood safety." *Transfusion medicine reviews* 34.2 (2020): 75-80.

[2]- Ren, Li-Li, et al. "Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study." *Chinese medical journal* 133.9 (2020): 1015.

[3]- Huang, Chaolin, et al. "Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China." *The lancet* 395.10223 (2020): 497-506.

[4]- Peeri, Noah C., et al. "The SARS, MERS and novel coronavirus (COVID-19) epidemics, the newest and biggest global health threats: what lessons have we learned?" *International journal of epidemiology* 49.3 (2020): 717-726.

[5]- Rothan, Hussin A., and Siddappa N. Byrareddy. "The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak." *Journal of autoimmunity* 109 (2020): 102433.

[6]- Bogoch, Isaac I., et al. "Pneumonia of unknown aetiology in Wuhan, China: potential for international spread via commercial air travel." *Journal of travel medicine* 27.2 (2020): taaa008.

[7]- Lu, Hongzhou, Charles W. Stratton, and Yi-Wei Tang. "Outbreak of pneumonia of unknown aetiology in Wuhan, China: The mystery and the miracle." *Journal of medical virology* 92.4 (2020): 401.

[8]- Shu, Yuelong, and John McCauley. "GISAID: Global initiative on sharing all influenza data–from vision to reality." *Euro surveillance* 22.13 (2017): 30494.

[9]- Pollock, David D., et al. "Viral CpG deficiency provides no evidence that dogs were intermediate hosts for SARS-CoV-2." *Molecular biology and evolution* 37.9 (2020): 2706-2710.

[10]- Tyrrell, D. A. J., and M. L. Bynoe. "Cultivation of viruses from a high proportion of patients with colds." *Lancet* (1966): 76-7.

[11]- Hasan, Md Mahmudul, et al. "A computational approach for predicting role of human microRNAs in MERS-CoV genome." *Advances in bioinformatics* 2014 (2014).

[12]- Giovanetti, Marta, et al. "The first two cases of 2019-nCoV in Italy: Where they come from?" *Journal of medical virology* 92.5 (2020): 518-521.

[13]- Paraskevis, Dimitrios, et al. "Full-genome evolutionary analysis of the novel corona virus (2019-nCoV) rejects the hypothesis of emergence as a result of a recent recombination event." *Infection, Genetics and Evolution* 79 (2020): 104212.

[14]- Banerjee, Arinjay, et al. "Bats and coronaviruses." *Viruses* 11.1 (2019): 41.

[15]- Li, Wendong, et al. "Bats are natural reservoirs of SARS-like coronaviruses." *Science* 310.5748 (2005): 676-679.

[16]- Hampton, Tracy. "Bats may be SARS reservoir." *Jama* 294.18 (2005): 2291-2291.

[17]- Li, Qun, et al. "Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia." *New England journal of medicine* (2020).

[18]- Carlos, W. Graham, et al. "Novel Wuhan (2019-nCoV) Coronavirus." *Am J Respir Crit Care Med* (2020): P7-P8.

[19]- Wu, Peng, et al. "Real-time tentative assessment of the epidemiological characteristics of novel coronavirus infections in Wuhan, China, as at 22 January 2020." *Euro surveillance* 25.3 (2020): 2000044.

[20]- Wan, Yushun, et al. "Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus." *Journal of virology* 94.7 (2020): e00127-20.

[21]- Jaimes, Javier A., et al. "A tale of two viruses: the distinct spike glycoproteins of feline coronaviruses." *Viruses* 12.1 (2020): 83.

[22]- Matsuyama, Shutoku, et al. "Enhanced isolation of SARS-CoV-2 by TMPRSS2-expressing cells." *Proceedings of the National Academy of Sciences* 117.13 (2020): 7001-7003.

[23]- Rothe, Camilla, et al. "Transmission of 2019-nCoV infection from an asymptomatic contact in Germany." *New England journal of medicine* 382.10 (2020): 970-971.

[24]- Nassar, MS1, et al. "Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: epidemiology, pathogenesis and clinical characteristics." *Eur Rev Med Pharmacol Sci* 22.15 (2018): 4956-4961.

[25]- Malave, Adriel, and Elamin M. Elamin. "Severe acute respiratory syndrome (SARS): lessons for future pandemics." *AMA Journal of Ethics* 12.9 (2010): 719-725.

[26]- Lin, Min-Han, et al. "Structural and functional characterization of MERS coronavirus papain-like protease." *Journal of biomedical science* 21.1 (2014): 1-8.

[27]- Azhar, Esam I., et al. "Evidence for camel-to-human transmission of MERS coronavirus." *New England Journal of Medicine* 370.26 (2014): 2499-2505.

[28]- van Doremalen, Neeltje, et al. "Host species restriction of Middle East respiratory syndrome coronavirus through its receptor, dipeptidyl peptidase 4." *Journal of virology* 88.16 (2014): 9220-9232.

[29]- Ambros, Victor. "The functions of animal microRNAs." *Nature* 431.7006 (2004): 350-355.

[30]- Bartel, David P. "MicroRNAs: genomics, biogenesis, mechanism, and function." *cell* 116.2 (2004): 281-297.

[31]- Esquela-Kerscher, Aurora, and Frank J. Slack. "Oncomirs—microRNAs with a role in cancer." *Nature reviews cancer* 6.4 (2006): 259-269.

[32]- Serban, Marinela, et al. "Spontaneous echo contrast of unexpected aetiology." *European Journal of Echocardiography* 7.3 (2006): 257-259.

[33]- Miao, Chenggui, et al. "MicroRNAs in type 1 diabetes: new research progress and potential directions." *Biochemistry and Cell Biology* 96.5 (2018): 498-506.

[34]- Perkins, Diana O., et al. "microRNA expression in the prefrontal cortex of individuals with schizophrenia and schizoaffective disorder." *Genome biology* 8.2 (2007): 1-11.

[35]- Sonkoly, Enikö, et al. "MicroRNAs: novel regulators involved in the pathogenesis of psoriasis?" *PloS one* 2.7 (2007): e610.

[36]- Latronico, Michael VG, Daniele Catalucci, and Gianluigi Condorelli. "Emerging role of microRNAs in cardiovascular biology." *Circulation research* 101.12 (2007): 1225-1236.

[37]- Janssen, Harry LA, et al. "Treatment of HCV infection by targeting microRNA." *New England Journal of Medicine* 368.18 (2013): 1685-1694.

[38]- Li, Yongsheng, et al. "Comprehensive analysis of the functional microRNA–mRNA regulatory network identifies miRNA signatures associated with glioma malignant progression." *Nucleic acids research* 41.22 (2013): e203-e203.

[39]- Cui, Feng-Mei, et al. "Radon-induced alterations in micro-RNA expression profiles in transformed BEAS2B cells." *Journal of Toxicology and Environmental Health, Part A* 76.2 (2013): 107-119.

[40]- Montag, Judith, et al. "Upregulation of miRNA hsa-miR-342-3p in experimental and idiopathic prion disease." *Molecular neurodegeneration* 4.1 (2009): 1-7.

[41]- Seo, G. J., et al. "Evolutionarily conserved function of a viral microRNA." *Journal of virology* 82.20 (2008): 9823-9828.

[42]- Melar-New, Marta, and Laimonis A. Laimins. "Human papillomaviruses modulate expression of microRNA 203 upon epithelial differentiation to control levels of p63 proteins." *Journal of virology* 84.10 (2010): 5212-5221.

[43]- Gupta, A., et al. "Anti-apoptotic function of a microRNA encoded by the HSV-1 latency-associated transcript." *Nature* 442.7098 (2006): 82-85.

[44]- Ura, Shunsuke, et al. "Differential microRNA expression between hepatitis B and hepatitis C leading disease progression to hepatocellular carcinoma." *Hepatology* 49.4 (2009): 1098-1112.

[45]- Omoto, Shinya, and Yoichi R. Fujii. "Regulation of human immunodeficiency virus 1 transcription by nef microRNA." *Journal of General Virology* 86.3 (2005): 751-755.

[46]- Dunn, Walter, et al. "Human cytomegalovirus expresses novel microRNAs during productive viral infection." *Cellular microbiology* 7.11 (2005): 1684-1695.

[47]- Sullivan, Christopher S., et al. "SV40-encoded microRNAs regulate viral gene expression and reduce susceptibility to cytotoxic T cells." *Nature* 435.7042 (2005): 682-686.

[48]- Seo, Gil Ju, Chun Jung Chen, and Christopher S. Sullivan. "Merkel cell polyomavirus encodes a microRNA with the ability to auto regulate viral gene expression." *Virology* 383.2 (2009): 183-187.

[49]- Qin, Zhao-ling, et al. "Silencing of SARS-CoV spike gene by small interfering RNA in HEK 293T cells." *Biochemical and biophysical research communications* 324.4 (2004): 1186-1193.

[50]- Rebolledo-Mendez, Jovan, et al. "Cross-kingdom sequence similarities between human micro-RNAs and plant viruses." *Communicative & integrative biology* 6.5 (2013): e24951.

[51]- Vaschetto, Luis María. "A putative miRNA in the spike gene of SARS-CoV-2 has perfect sequence identity to both the forward and reverse complementary strands of hsa-mir-8055 involved in T-cell response to antigen." (2020).

[52]- Sardar, Rahila, et al. "Comparative analyses of SAR-CoV2 genomes from different geographical locations and other coronavirus family genomes reveals unique features potentially consequential to host-virus interaction and pathogenesis." *BioRxiv* (2020).

[53]- Fang, Lei, George Karakiulakis, and Michael Roth. "Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection?" *The lancet respiratory medicine* 8.4 (2020): e21.

[54]- Chen, Lai-Jiang, et al. "The ACE2/apelin signalling, microRNAs, and hypertension." *International journal of hypertension* 2015 (2015).

[55]- Bartel, David P. "Metazoan micrornas." *Cell* 173.1 (2018): 20-51.

[56]- Krol, Jacek, Inga Loedige, and Witold Filipowicz. "The widespread regulation of microRNA biogenesis, function and decay." *Nature Reviews Genetics* 11.9 (2010): 597-610.

[57]- Zhdanov, Vladimir P. "Intracellular miRNA or siRNA delivery and function." *BioSystems* 171 (2018): 20-25.

[58]- Rakhmetullina, Aizhan, et al. "The miRNA complexes against coronaviruses COVID-19, SARS-CoV, and MERS-CoV." (2020).

[59]- Demirci, Müşerref Duygu Saçar, and Aysun Adan. "Computational analysis of microRNA-mediated interactions in SARS-CoV-2 infection." *PeerJ* 8 (2020): e9369.

[60]- Zhang, Sen, et al. "Up-regulation of microRNA-203 in influenza A virus infection inhibits viral replication by targeting DR1." *Scientific reports* 8.1 (2018): 1-15.

[61]- Komatsu, Kiyoshi, et al. "Human homologue of S. pombe Rad9 interacts with BCL-2/BCL-x L and promotes apoptosis." *Nature cell biology* 2.1 (2000): 1-6.

[62]- Liu, Zhi, et al. "Implications of the virus-encoded miRNA and host miRNA in the pathogenicity of SARS-CoV-2." *arXiv preprint arXiv:2004.04874* (2020).

[63]- Balmeh, Negar, et al. "Predicted therapeutic targets for COVID-19 disease by inhibiting SARS-CoV-2 and its related receptors." *Informatics in medicine unlocked* 20 (2020): 100407.

[64]- Fani, Mona, et al. "The role of miRNAs in COVID-19 disease." *Future Virology* 16.4 (2021): 301-306.

[65]- Ivashchenko, Anatoliy Timofeevich, et al. "How miRNAs can protect humans from coronaviruses COVID-19, SARS-CoV, and MERS-CoV." *BIOINFORMATICS OF GENOME REGULATION AND STRUCTURE/SYSTEMS BIOLOGY (BGRS/SB-2020)*. 2020.

[66]- Khan, Md, et al. "Epigenetic regulator miRNA pattern differences among SARS-CoV, SARS-CoV-2, and SARS-CoV-2 world-wide isolates delineated the mystery behind the epic pathogenicity and distinct clinical characteristics of pandemic COVID-19." *Frontiers in genetics* 11 (2020): 765.

[67]- Nersisyan, Stepan, et al. "Potential role of cellular miRNAs in coronavirus-host interplay." *PeerJ* 8 (2020): e9994.

[68]- Chan, Agnes P., Yongwook Choi, and Nicholas J. Schork. "Conserved genomic terminals of SARS-CoV-2 as coevolving functional elements and potential therapeutic targets." *MSphere* 5.6 (2020): e00754-20.

[69]- Arisan, Elif Damla, et al. "The prediction of miRNAs in SARS-CoV-2 genomes: hsa-miR databases identify 7 key miRs linked to host responses and virus pathogenicity-related KEGG pathways significant for comorbidities." *Viruses* 12.6 (2020): 614.

[70]- Demirci, Müşerref Duygu Saçar, and Aysun Adan. "Computational analysis of microRNA-mediated interactions in SARS-CoV-2 infection." *PeerJ* 8 (2020): e9369.

[71]- Sardar, Rahila, et al. "Comparative analyses of SAR-CoV2 genomes from different geographical locations and other coronavirus family genomes reveals unique features potentially consequential to host-virus interaction and pathogenesis." *BioRxiv* (2020).

[72]- Hosseini Rad SM, Ali, and Alexander D. McLellan. "Implications of SARS-CoV-2 mutations for genomic RNA structure and host microRNA targeting." *International journal of molecular sciences* 21.13 (2020): 4807.

[73]- Liu, Zhi, et al. "Implications of the virus-encoded miRNA and host miRNA in the pathogenicity of SARS-CoV-2." *arXiv preprint arXiv:2004.04874* (2020).

[74]- Chauhan, Neeraj, et al. "COVID-19: Fighting the invisible enemy with microRNAs." *Expert Review of Anti-Infective Therapy* 19.2 (2021): 137-145.

[75]- Widiasta, Ahmedz, et al. "Potential role of ACE2-related microRNAs in COVID-19-associated nephropathy." *Non-coding RNA research* 5.4 (2020): 153-166.

[76]- Arora, Shweta, et al. "Unravelling host-pathogen interactions: ceRNA network in SARS-CoV-2 infection (COVID-19)." *Gene* 762 (2020): 145057.

[77]- Liu, Zhi, et al. "Implications of the virus-encoded miRNA and host miRNA in the pathogenicity of SARS-CoV-2." *arXiv preprint arXiv:2004.04874* (2020).

[78]- Mishra, Paras K., Ritesh Tandon, and Siddappa N. Byrareddy. "Diabetes and COVID-19 risk: a miRNA perspective." *American Journal of Physiology-Heart and Circulatory Physiology* 319.3 (2020): H604-H609.

[79]- Fulzele, Sadanand, et al. "COVID-19 virulence in aged patients might be impacted by the host cellular microRNAs abundance/profile." *Aging and disease* 11.3 (2020): 509.

[80]- Guterres, Alexandro, et al. "What is the potential function of microRNAs as biomarkers and therapeutic targets in COVID-19?" *Infection, genetics and evolution* 85 (2020): 104417.

[81]- Chow, Jonathan Tak-Sum, and Leonardo Salmena. "Prediction and analysis of SARS-CoV-2-targeting MicroRNA in human lung epithelium." *Genes* 11.9 (2020): 1002.

[82]- Demongeot, Jacques, and Hervé Seligmann. "SARS-CoV-2 and miRNA-like inhibition power." *Medical Hypotheses* 144 (2020): 110245.

[83]- Nepotchatykh, Evguenia, et al. "Profile of circulating microRNAs in myalgic encephalomyelitis and their relation to symptom severity, and disease pathophysiology." *Scientific reports* 10.1 (2020): 1-13.

[84]- Fu, Yong, Jiangning Chen, and Zhen Huang. "Recent progress in microRNA-based delivery systems for the treatment of human disease." *ExRNA* 1.1 (2019): 1-14.