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Review article

Mesenchymal stem cell immunomodulation and regeneration therapeutics as an ameliorative approach for COVID-19 pandemics

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ABSTRACT

The severe acute respiratory syndrome-novel coronavirus mediated COVID-19 has been recently declared a pandemic by the World Health Organization. The primary target of the SARS-CoV-2 virus is the human lungs governed by the ACE-2 receptor of epithelial type II cells/endothelial cells, which promote modulation of the immune response of host cells through generating cytokine storm, inflammation, severe pneumonia symptoms, and secondary complications such as acute respiratory distress syndrome. Although numerous antiviral and anti-parasitic drugs are under clinical trials to combat this pandemic, to date, neither a specific treatment nor any successful vaccine has been established, urging researchers to identify any potential candidate for combating the disease. Mesenchymal stem cells own self-renewal, differentiation, homing, immunomodulation and remains unaffected by the coronavirus on the virtue of the absence of ACE-2 receptors, indicating that MSC's could be used an ameliorative approach for COVID-19. MSCs have shown to combat the disease via various pathways such as repairing the lung epithelial and endothelial cells, reducing hyperimmune response, maintaining the renin-angiotensin system. Although MSCs-based treatment approaches for COVID-19 is still under consideration with limited data, many human clinical trials of MSC's has been initiated to explore their potential for COVID 19 treatment. The current review summarizes and emphasizes on how MSC's modulate the immune response, can repair the lungs from the impact of the virus, and various aspects of MSC's as a remedial source for COVID-19, to provide better insight for biomedical researchers and for those who are fascinated by stem cells as a therapeutic approach.

1. Introduction

In late December 2019, the World Health Organization (WHO) noticed few clinical cases reported from Wuhan City of China, suffering from respiratory infections and pneumonia. These cases, which were related to the Wuhan seafood market, were initially misdiagnosed as common flu but later considered having unidentified etiology and eventually lead to immediate closure and sanitization of this market. After further investigations and research, scientists revealed that the causative agent of this disease in these patients was a novel coronavirus (nCoV), similar to the coronavirus causing Severe Acute Respiratory Syndrome, hence called SARS novel Coronavirus-2 (SARS-nCoV-2) under the family *Coronaviridae* and shares 89.1% homology to SARS-CoV [1]. Later this virus nCoV initiated disease was designated as coronavirus disease 2019 (COVID-19).

The impact of COVID-19 rapidly became so diverse and global, that by mid-March 2020 WHO declared the disease as a global public health care emergency and a pandemic. As per the WHO, the total confirmed COVID-19 cases reported globally were 33,842,281 followed by 1,010,634 deaths till 1 October 2020 [2]. The main pathological

Abbreviations: ACE2, Angiotensin-converting enzyme 2,; Ag I, Angiotensin I; ARSD, Acute respiratory distress syndrome; AT1 R, Angiotensin receptor type I; AT-II, Alveolar epithelial type 2 cells; CD, Cluster of differentiation; CD209L, C-type 209 lecithin; CM, Conditioned media; COVID-19, Coronavirus disease 2019; DAMPs, Damage associated molecular patterns; G-CSF, Granulocyte colony-stimulating growth factor; GVHD, Graft-versus-host disease; HLA, Human leukocyte antigen; IDO, Indoleamine 2,3-dioxygenase; IFN- β, Interferon- β; Ig E, Immunoglobulin E; IL, Interleukin; IRF-3, Interferon regulatory factor-3; KGF, Keratinocyte growth factor; MCP-1, Monocyte chemoattractant protein; MERS-Cove, Middle East respiratory syndrome coronavirus; MIP, Macrophage inflammatory protein; MSC's, Mesenchymal stem cells; MV's, Microvesicles; NK, Natural killer; PAMPs, Pathogen-associated molecular pattern; PGE-2, Prostaglandin E2; RAGE, Receptor for advanced glycation end products; RAS, Renin-angiotensin system; RT-qPCR, Reverse transcription real-time nucleic acid polymerase reaction:; SARS-CoV, Severe acute respiratory syndrome coronavirus; SARS-CoV-2, Severe Acute Respiratory Syndrome novel Cornovirus-2; SLE, Systemic lupus erythematous; TGF- β, Transforming growth factor- β; TNF-α, Tumour necrosis factor; WHO, World health organization

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features of COVID-19 are fairly similar to those observed in SARS, but, in severe cases, these can lead to Acute respiratory distress syndrome (ARDS), acute lung injury (ALI) with lung inflammation and edema along with hyaline membrane formation. COVID-19 patients have to be given supportive treatment in complicated and severe cases that need clinical interventions such as ventilation, antipyretics, and few repurposed drugs (for example remdesivir). Apart from these, one has to rely on their immune system. Various treatment strategies are being opted by clinicians all across the globe to counterattack this disease however neither a substantial treatment nor a promising vaccine has been developed so far. Although few potential vaccines have been predicted which still requires further investigations and clinical trials before becoming available to the public. With no established antiviral medication or vaccine, COVID-19 accounts for 0.7% to 15.4% mortality rate and also poses other unprecedented concern for the economy as well as health, leading to drawing the interest of various scientists to combat and manage the disease with utmost priority. Hence, alternative promising therapies are required to tackle the pandemic by searching for better treatment and recovery options for patients of COVID-19.

Stem cells owing to the properties of self-renewal, differentiation, and regenerative potential [3–5], can be used as an alternative treatment for COVID-19. As proven by various studies, stem cells possess immune-modulatory activity, which can favorably play a crucial role in combating this pandemic disease, as the causative agent manifests severe immune response, molecular mimicry of host cell epitope, and epitope spreading, leading to the up-regulation of immune response and consequently the destruction of the host cells [6,7]. As per the records, stem cells have shown tremendous attainments of goals in treating numerous ailments ranging from blood disorders, cardiovascular, neuronal, kidney to pulmonary disorders including lung fibrosis, ALI, and ARDS [7–9]. The enormous immunomodulatory and regenerative potential of stem cells has already started attracting clinicians and researchers, in finding their role in combating and managing patients suffering from COVID-19 and how they can be exploited to ameliorate after-effects of this disease. Although no approved stem cell-based prevention or treatment plan has come up yet, clinical trials using this approach have already begun worldwide by various therapeutic companies and hospitals. Preliminary results suggest that mesenchymal stromal/stem cells (MSCs) or their derivatives appear to be an alternative promising therapy for COVID-19. In this review article, we are taking the initiative in summarizing the current use and future prospective of the immunomodulatory and regenerative therapeutic potential of mesenchymal stem cells for the treatment of COVID -19.

1.1. COVID-19 and its instigation

COVID-19 outbreak was started from Wuhan City of China in December 2019 where a group of people reported pneumonia-like symptoms such as sore throat, chest pain, cough, sneeze, and in severe cases required ventilation for breathing due to breathing shortness. At first, these were misdiagnosed as seasonal flu, also the etiology of such pneumonia-like symptoms was not known. After research and data obtained from the patients, the epidemiologists found that the cluster was directly or indirectly connected to the Hunan seafood market of Wuhan [10], which in turn also gave the hypothesis of zoonotic disease transmission. As the symptoms of patients were closely related to coronaviridae family-related diseases such as SARS-CoV, Middle East respiratory syndrome coronavirus (MERS-CoV), and HINI influenza that occurred in the past, the samples were processed and analyzed with a genome database of different viruses and also with coronaviridae family. It was found that the pneumonia-like symptoms were caused by the virus, whose genome shared 89.1% homology to SARS-CoV [1]. Hence, the virus was first termed as SARS-novel CoV (SARS-CoV-2). The phylogenetic similarity of the virus suggested that bats could be its reservoir, which was later proved by extracting samples from different bat species [11].

1.2. Transmission of SARS-CoV-2

SARS-CoV-2 belongs to the beta group genera of the *Nidovirales* order under *the Orthocoronavirinae* subfamily of *the* family Coronaviridae [12]. It is an enveloped virus where a single-stranded ribonucleic acid genome is enclosed by structural components such as nucleocapsid protein (N), envelope protein (E), membrane protein (M), and spike (S) glycoprotein present on the envelope [13]. The human to human transmission of COVID -19 infected 33,842,281 followed by 1,010,634 deaths till 1 October 2020 worldwide [14]. Spreading of the disease is through directly sneezing or coughing into the environment and releasing the virus via droplets or aerosols into the surrounding and thus making a healthy individual vulnerable to the disease once they inhale contaminated air. Also, one can be affected when exposed to close contact with an infected person [15].

1.3. Clinical manifestations

Based on the severity of symptoms, clinical manifestations of a SARS-CoV-2 infected person can be categorized into three forms starting from asymptomatic to critical. In a report submitted by China, out of 72,314 suspected and confirmed cases of COVID-19, 81% were asymptomatic or presented mild pneumonia symptoms such as cough, diarrhea, fever with chills, breath shortness, anosmia (loss of taste), which can be categorized as mild COVID-19 [16]. The disease was severe in 14% of total cases in which the person experienced prevalent pulmonary inflammation and edema, infiltrate in the upper lobe caused dyspnea and hypoxemia, hyaline membrane formation, pulmonary fibrosis, low lymphocyte count, inflammatory cytokine storm, and ALI or ARDS. Secondary clinical manifestations which account for 5% of total cases governed by secondary complications such as bacterial infection, acute cardiac injury, shock, acute kidney infection, chronic respiratory failure, cardiomyopathy, organ failure and sepsis, resulted into higher mortality rate [10].

1.4. Mode of entry and pathophysiology of SARS-CoV-2

The Transmembrane Serine Protease 2 (TMPRSS2), also involved in Influenza, modify the SARS-CoV-2 spike protein, which is mandatory for viral ingress into host cells [17], The virus-mediated entry to host cells could be via infusion with the host plasma membrane, clathrin-mediated endocytosis or receptor-mediated [18]. Among these, Receptor-mediated invasion is the most common. The host cellular receptors like angiotensin-converting enzyme 2 (ACE2) and C-type lecithin (CD209L) acts as an entry point for the virus.

Angiotensin-converting enzyme-2 (ACE-2) primarily present on pulmonary epithelial cells, enterocytes, and endothelial cells [19] act as a cellular receptor for the binding of the spike protein of the virus, which becomes the first stage of the pathogenesis of COVID-19. Remarkably, ACE2 is absent on bone marrow cell, stem cells, B and T lymphocytes, macrophages, lymph nodes, thymus, and spleen [20]. ACE-2 convert angiotensin I (Ag I) into Ag II. Ag II regulates the Renin-angiotensin system (RAS), cytokine generation, and vascular permeability. Disruption of the AgII level leads to various manifestations [21] as described in Fig. 1. As endothelial cells play a crucial role in the body physiologic process, the viral entry in these cells via ACE-2 receptors leads to inflammation and endothelitis, which results in vascular dysfunction through microvascular thrombosis, which may lead to organ failure [22,23]. It has been studied that in the early phase of infection, SARS-CoV blocks activation of IFN- β, by localizing interferon regulatory factor-3 (IRF-3) from cytosol to nucleus [24].

In the case of SARS-CoV, the virus weakly sensitizes the Mast cells, which produce IFN-γ and a small amount of Immunoglobulin E that binds to its receptor FceRI, resulting in the generation of pro-inflammatory cytokines secretion such as Interleukin (IL)-6, IL-1, IL-13, tumor necrosis factor- α (TNF-α), chemokines secretion (MCP-1,

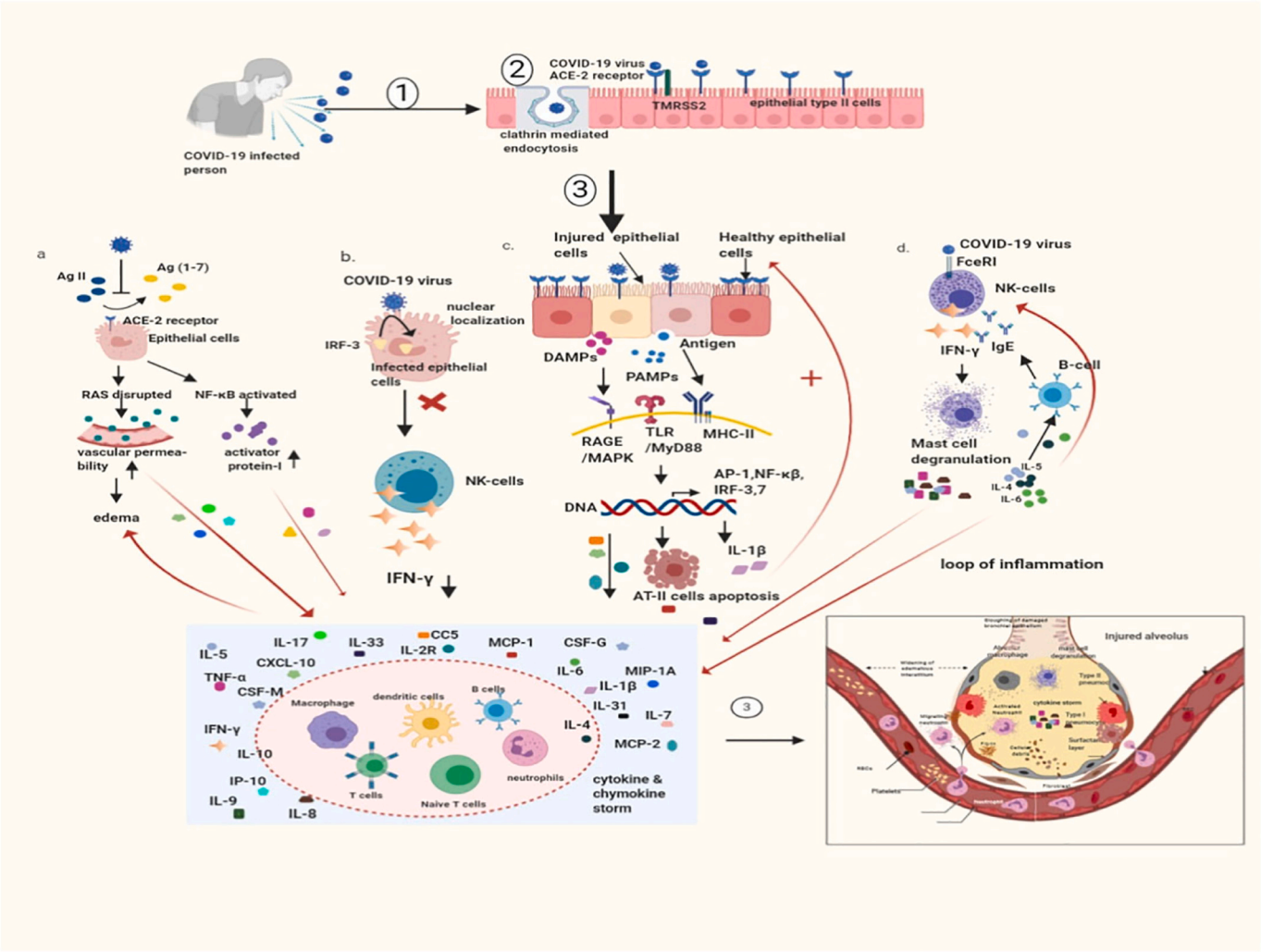

Fig. 1. Pathogenesis and immunomodulation of COVID -19: 1. The infected person spread the disease via a cough or sneeze to a healthy individual. 2. The Entry of virus via clathrin-mediated endocytosis or receptor-mediated, in later the virus spike protein binds to ACE-2 receptor of pulmonary epithelial cells and protease TMRSS2 mediated activation of the spike protein. 3. Generation of cytokine storm by innate and immune cells: a. Upregulation Ag II due to low level of ACE-2 receptor which mediates activation of NF-kβ and AP-I signaling pathway via AT- 1 receptor resultant in vasodilation, edema, and cytokine secretion. b. Nuclear localization of IRF-3 by virus which reduces the production of IFN-γ. c. Activation of toll-like receptor, RAGE and MHC-II via generation of DAMP's from injured pneumocytes and through PAMP's which leads to activation of NF-κβ, IRF-3/7, AP-1 signaling pathway. d. Weak sensitization of mast cells by virus releases a small amount of Ig E and IFN-γ followed by the attraction of NK cells, macrophage, and B-cells which further elevates the secretion of a cytokine storm. 4. Overview of damaged alveolus resulted from cytokine storm and hyperactive immune cells. The figure is made via biorender application: https://biorender.com/)

CXC18, CXCL10) and alarmin. Production of IFN-γ by mast cells attract natural killer (NK) cells and activate NK-mediated cytotoxicity [25]. Activation of damage associated molecular patterns (DAMPs) also called as “alarmin” or pathogen-associated molecular pattern (PAMPs) activate toll-like receptor or receptor for advanced glycation end products (RAGE), which lead to release of chemokine's and cytokines which exacerbate innate immune response. Pathogenesis of COVID-19 accomplishes by numerous molecular interactions with host cells, which leads to ALI or ARSD as depicted in Fig. 1.

SARS-CoV-2 shared the homology in pathogenesis to other viral diseases (specially SARS-CoV) or autoimmune disorders and elicit an immune response in the similar manner. Thus, in COVID-19 as well, the hyper-activation of immune response occurs which results in generating a cytokine storms. T-helper-1 (Th1) cells get activated by elevated levels of IL1B, IFNγ, IP10, and MCP1 secreted by NK cells, mast cells and macrophages. Additionally, critically ill patients have been reported with a high level of granulocyte colony-stimulating growth factor (GCSF), Macrophage inflammatory protein (MIP1A), TNFα, IL-2R and IL-6. COVID-19 also induces the pro-inflammatory release of IL-4 from T-helper-2 (Th2) to suppress inflammation [26]. Inflammatory cytokine storm in patients contributes to secondary complications such as sepsis, hyper-coagulability, ALI, ARDS and lung fibrosis.

Overall, the escaping of the virus from immune cells, hyperimmune activation of innate and adaptive cells, excessive accumulation of chemokines and cytokines secreted from pulmonary cells as well as modulation of ACE-2 expression may attribute to the pathogenesis of COVID-19, and targeting these physiological processes may be used in combating the disease. Keeping this in mind various researches are undergoing and numerous anti-COVID19 drugs and vaccines are under different phases of the clinical trials. Clinicians are repurposing various drugs such as Remdesivir, Duvelisib, Deferoxamine, Favipiravir Hydroxychloroquine, Isotretinoin, and Azithromycin, Ritonavir Pill as well as plasma-based SARS-CoV-2 convalescent approach [27]. Subsequently, along with the above-said approaches, researchers and clinicians are now shifting towards alternate approaches including mesenchymal stem cells with immunomodulatory and regenerative properties [28] that can become a remedial source to treat COVID-19 and its after-effects.

1.5. Mesenchymal stem cells (MSCs)

In the past decade, owing to enormous potential, self-renewal and differentiation properties, stem cells have already revealed a promising role in treating and combating numerous life-threatening diseases and became a pivot area of modern research. Based on the source of isolation or origin, stem cells can be divided into three categories viz. embryonic, fetal and adult [3]. Although fetal and embryonic stem cells have a higher potential than adult stem cells, the later are more implicated in experimental biology due to their widespread availability and less ethical issues. Bone marrow-derived, adipogenic, human dental pulp and umbilical cord blood are among numerous sources of adult stem cells, which plays a crucial role in regenerative medicine. Moreover, these stem cells can be isolated and saved in stem cell banks under ultra-low temperature for many years without hampering their potential. Umbilical cord blood and bone marrow are the reservoirs of both hematopoietic stem cells (form blood lineage cells) and Mesenchymal stem cells (MSCs), the later are the utmost explored and exploited categories of stem cells in treating various disorders [29].

Mesenchymal stem cells, named due to their presence in the mesodermal niche, are multipotent. They are also termed as mesenchymal stromal cells, if they fulfill the minimum criteria of adherent property, presence of CD105, CD73, and CD90, absence of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR cell surface markers as well as gives rise to descendant lineages including chondrocytes, osteocytes, adipocytes, and myocytes [30] as characterized by the International Society of Stromal Therapy (ISCT) in 2005 [31]. In general, Mesenchymal stem cells term can be used for plastic adherent fibroblast shaped cells, which fulfills the criteria of stem cells and MSC acronym is used for both mesenchymal stem as well as stromal cell types [32]. However, the name of MSCs is still controversial. Caplan [33], recommended changing the Mesenchymal stem cell name to “medicinal signaling cells” as indeed these cells show the property of homing and secrete bioactive factors that possess the immunomodulatory and regenerative potential that act as drugs in situ and has shown site-specific therapeutic outcomes. It has been shown that infused exogenous MSCs signals resident stem cells of the patient to repair the damage via their bioactive factors instead of undergoing their differentiation [33]. For research as well as for clinical purposes, ample amounts of MSCs can be isolated from the embryo, fetus as well as adult stem cell sources, which include bone marrow, umbilical cord blood, adipose tissue, menstrual blood, Wharton's jelly, amniotic fluid and Human Deciduous teeth.

1.6. MSCs as a treatment approach for COVID-19

Mesenchymal stem cells could play a pivotal role in combating COVID-19 because of its immunomodulation and regenerative potential as depicted in Fig. 2. From the past many years, the role of MSC's as immunomodulation and its regenerative potential have been relentlessly investigated. Use of MSCs as a regenerative medicine has been well-established but, needs further investigation for the management and treatment of steroid-resistant graft-versus-host disease (GVHD), systemic lupus erythematosus (SLE), ARDS, chronic obstructive pulmonary disease (COPD), liver cirrhosis, pneumonia and Lung fibrosis, in various in-vitro experiments, animal model systems [34–36] and human in-vivo studies [8,37–40]. Numerous preclinical and clinical studies claimed that MSCs act as an immunosuppressive agent for the treatment of GVHD [41]. MSCs shows potential to escape recognition by CTL or NK cells, inducing allogeneic T-cell tolerance, attenuate T-cell proliferation via reducing Th1 and Th17 activation, which further compromises the immune response. This is due to lack in the expression of human leukocyte antigen (HLA) class II, co-stimulatory molecules (B71, CD40L, B72) and low-level expression of HLA-I and LFA-3 in these cells [42]. MSC's behave as an immunosuppressive agent even after these cells have been immunosuppressed by host cells via apoptosis. The highly Cytotoxic T–cells induce apoptosis of MSCs, which in turn release indoleamine 2,3-dioxygenase (IDO) by phagocytic cells needed for the clearance of apoptotic MSC bodies. Released IDO by phagocytic cells acts as an immunosuppressents, which sequentially suppresses the graft rejection mechanism [43]. Thus, MSCs help in overcoming the major issue confronted in GVHD, which is the rejection of graft by the cytotoxic effect of immune cells and also shows the potency of homing at the site of inflammation [44].

MSCs can elicit a shielding effect for combating COVID-19 by involving multiple pathways as depicted in Fig. 3. MSC's stimulate the immunomodulatory activity by secreting various juxtracrine and paracrine molecules such as transforming growth factor β (TGF-β), IDO, Human leukocyte antigen isoform (HLA-G5), prostaglandin E2 (PGE2) and IL6 [45]. These factors act on modulating signaling pathways such as NO, which inhibit the phosphorylation of STAT-5, conversion of tryptophan into kynurenine by IDO, which subsequently suppresses the T-Cell proliferation. In one of the studies, MSC's immunomodulatory activity was determined by culturing them with immune cells and measuring the cytokine profiles released by these cells. It has been found that MSC's decrease the activity of DC1 pro-inflammatory cytokine profile; increase the anti-proliferative cytokine profile of DC2; reduces the IFN-γ released from NK cells and Th1; elevates IL-4 released by Th-2 and elevates proliferation of Treg cells [46]. One of the paracrine factors, PGE2 proved vital activity in MSC's immunosuppression [47]. MSCs modulates immune cells such as CD4+, CD8+, DC cells, macrophages, and NK Cells, which suppresses the cytokine storm-generated via COVID -19 infection and results in increasing the life expectancy of an infected person [48].

As MSCs act via secreting paracrine, juxtacrine molecule and microvesicles, thus MSCs conditioned media can also be utilized as immunosuppressive therapy for COVID-19. This perception is congruent with the previous study, which showed promising results in treating COPD with MSCs conditioned media, where the presence of secreted micro-vesicles (MVs) was confirmed [49]. MVs are membrane vesicles that exhibit various receptors like MHC-I, tetraspanins, cell-cell adhesion receptors, and the presence of cytoplasmic content such as Hsp, mRNA, microRNA and a set of protein lipids. [50]. Monsel et al. (2015) depicted that MVs reduces the effect of pneumonia induced ALI via enhancing monocytes mediated phagocytosis. This phenomenon helps in clearing bacteria; elevates secretion of keratinocyte growth factor release via mKGF which reduce endotoxin mediated alveolar damage; suppresses cytokine-induced lung injury; polarizes M1 macrophage to M2 macrophage via reducing mRNA for inducible nitric oxide synthase and increasing level of transglutaminase 2 forming mRNA when MSCs cultured supernatant media was administered. CD44 is found to be essential for MVs uptake by alveolar and monocytes. mCOX2 in MV's also mediates the synthesis of PGE2 and its up-regulation leading to the modulation of immune response [51]. Apart from using MSCs conditioned media, direct infusion of MSCs-released exosomes which are a subtype of MV's can be used to combat COVID-19. In a study conducted by Sengupta et al. (2020) it was depicted that the infusion of MSCs-released exosomes into severe to moderate COVID-19 patients reduces the effect of lymphopenia, increase neutrophil counts, decreases C-reactive protein and helps in reconstituting immune activity against SARS-CoV-2 [52].

MSCs also play a vital role in targeting ACE-2 mechanisms, which is essential for SARS-CoV-2 pathogenesis. As depicted by various scientists, ACE-2 hampered RAS via deregulated Ag II level, which leads to various complications which consequently were resolved by direct infusion of ACE-2 negative mesenchymal stem cells as recently proven by Leng et al.(2020), in a pilot study, where results depicted recovery of COVID-19 patients with pneumonia [48]. MSCs have the potential to differentiate into alveolar epithelial type 2 cells (AT-II cells), also known as type II lung pneumocytes [53,54]. ACE-2 receptors are expressed by AT-II cells, which are subsequently deregulated by the virus entry and initiating the apoptosis of neighboring AT-II cells by modulating the immune system hence generating a positive loop of

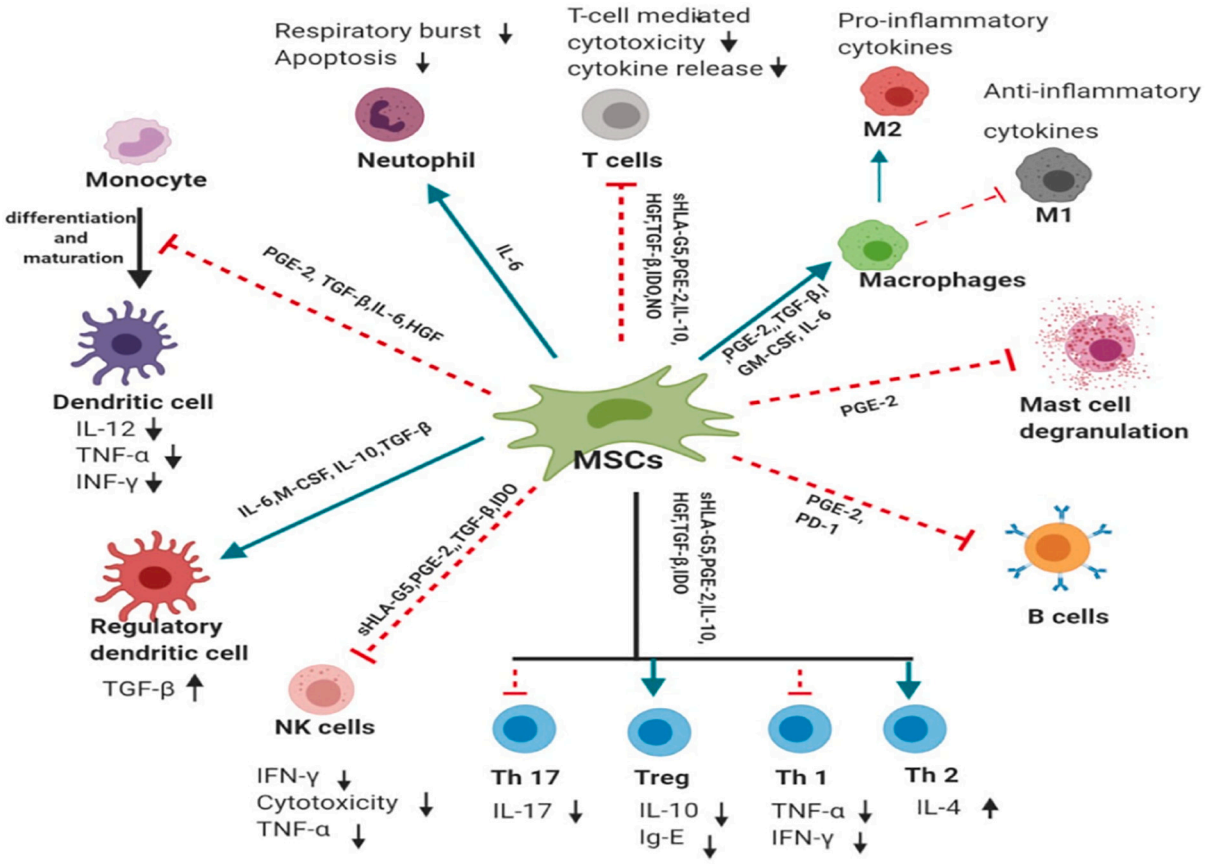

Fig. 2. Immunomodulation activity of MSC's on innate and adaptive immune cells: MSC's stimulate the immunomodulatory activity by secreting various juxtracrine and paracrine molecules such as IDO, prostaglandin E2 (PGE2), transforming growth factor β (TGF- β), Human leukocyte antigen isoform (HLA-G5), interleukin -6, indoleamine 2,3-dioxygenase (IDO), granulocyte or macrophage colony-stimulating growth factor, Nitric Oxide (NO). MSC's inhibit proliferation of NK cells, Th17, mast cell degranulation, antibody secretion of B-cells, T-cell mediated cytotoxicity, maturation of monocytes into dendritic cells, and maturation of macrophage into M1. On the other hand, MSC's activate pro-inflammatory cytokines by activating Th-2, Treg cells, generation of regulatory dendritic cells, and maturation of macrophage into M2 cells. The figure is made via biorender application: https://biorender.com/).

inflammation between these cells. Although there are controversies whether MSCs directly differentiated in-vivo or signals native stem cells to differentiate, still by knowing that MSCs have differentiation potential into AT-II cells, proven by Huang et al. (2014), in a pulmonary fibrosis mouse model [55], keeping this in mind, it can be suggested that MSC's infusion could be used to combat COVID-19. Alternatively, differentiated AT-II like cells could also be administered directly to fasten the response mediated by these cells. Infused MSCs also induce lung progenitors cell differentiation in bronchopulmonary dysplasia and reduces lung injury from hyperoxic conditions [56]. Apart from immunomodulation, regenerative and homing potential, interestingly, the drawback of MSC population entrapment in the lung during intravenously administered systemic infusion [57] could become an advantage in treating COVID-19 pneumonia, where the main target of the virus is the lungs. MSC's entrapment potential in the lungs would play a vital role in recovering inflamed lung microenvironment, lung fibrosis, cytokine storm, damaged epithelial and endothelial cells via its immunomodulate potential.

MSC's protect themselves from host cells via releasing isoform of human leukocyte antigen HLA-G5, which modulates the immune response. HLA-G5 suppresses NK lytic activity and IFN-γ Secretion; elevates the production of pro-inflammatory cytokine IL-10, which creates an allogenic microenvironment to inhibit T cell-mediated immunity; activates $CD4^{+}CD25^{high}FOXP3^{+}$ regulatory T cells [58]. As HLA-G5 enhances MSC's counterattack effect against the virus thus, it could be used as a preconditioned factor to enhance MSC's activity. Preconditioning of MSC's with Conditioned media has revealed to enhance the paracrine effect of MSC's in treating lung injury [59]. MSC's could be infused with IFN-β to mild disease patients as the viral entry inhibit the production IFN incongruent to the pathogenesis of SARS-CoV and skip the initial response of cells leading to an increase in viral load and which hamper the immune system [24]. So, if viral replication at the initial phase can be controlled or inhibit, mortality and complications related to the disease can be managed.

To date, the complete depiction of the use of MSCs as an immunomodulator as well as the entire pathology of COVID-19 is still unclear. Reformist work is needed by scientists to understand both. Thus, MSCs or differentiated AT-II like cells can be exploited as an in-vitro model system to study the pathology of the virus, the production and test the vaccines as these cells are easy to cultivate, accessible from various sources, and carry less ethical issues. As a model system, MSCs could also be used to produce antibodies against the virus and deduce the complete underlying mechanism of its action for treating COVID-19.

Clinical phase trial results of MSC's transplanted in H7N9 influenza induced ARDS or ARSD shows reduce mortality in the treated patients compared to the control groups [9,60], which raises hopes that MSCs can be used as a feasible approach of COVID-19 treatment. MSCs from various sources are already under preclinical and clinical approaches by numerous clinicians and researchers to mine out the complete potential of stem cells in treating COVID-19 disease. Sources and types of stem cells used in clinical trials are listed and depicted in Fig. 4 [61]. Apart from the umbilical cord as a source, dental stem cells are also reported in various clinical trials. Stem cells from Human Deciduous teeth (SHED) can also serve as a potential source for MSCs [62]. To combat

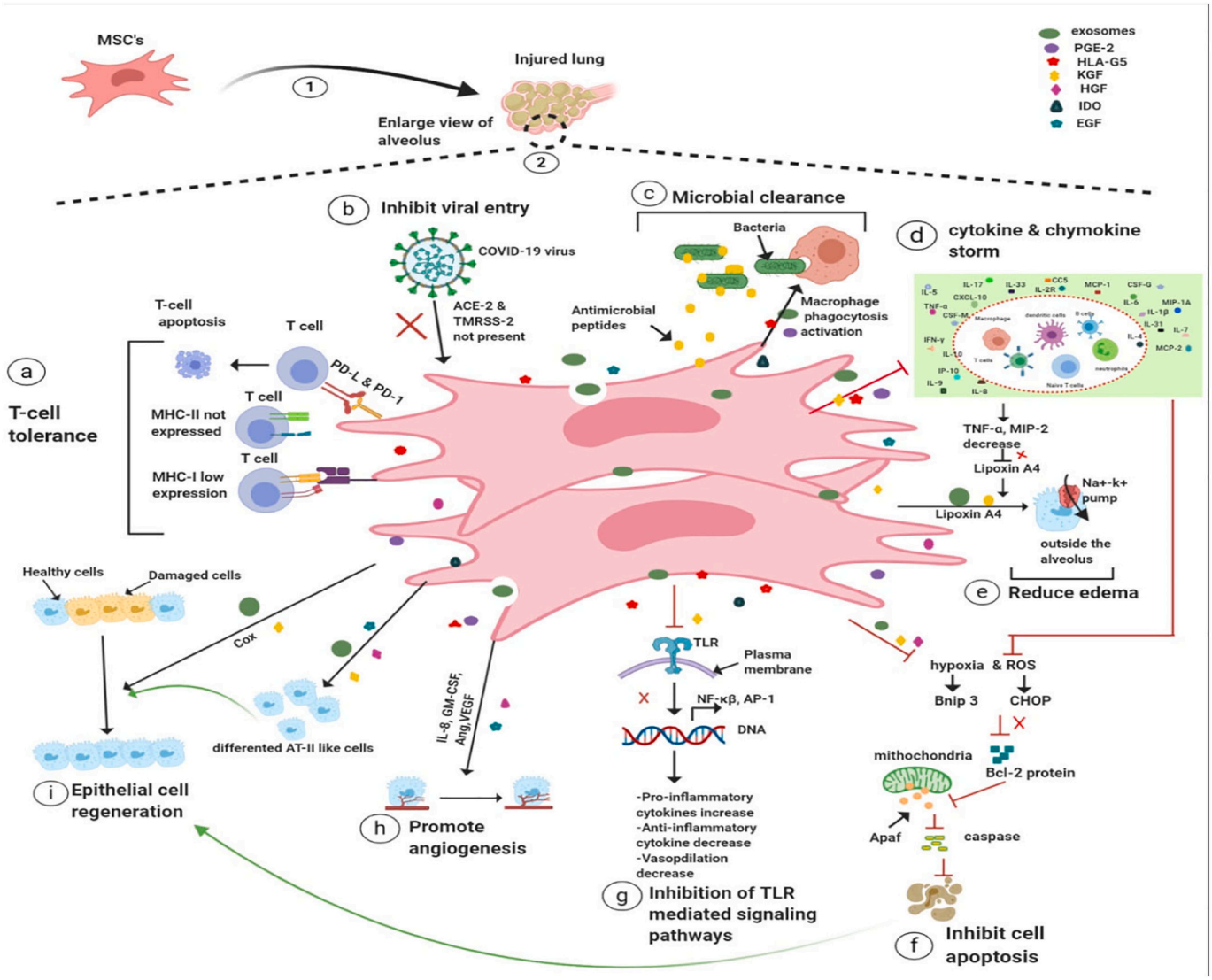

Fig. 3. Mode of action of MSC's for treating COVID-19: 1.Ifusion of MSC's 2. MSC's immunomodulation and regenerative potential in the inflamed lung after MSC's infusion. a. Infused MSC's generate T-cell tolerance thus escaping host T-cell mediated rejection. b. MSC's inhibit viral entry as they lack ACE-2 and TMRSS2. c. MSC's or exosomes mediate secondary microbial infection in COVID-19 patients by secreting antimicrobial proteins such as defensin and by activating the phagocytosis mode of macrophage. d. MSC's inhibit the major pathway that is cytokine storm by modulating the immune cells as described in Fig. 2. e. MSC's mediate the clearance of lung fluid by activating the Na+-K+ pump via exosomes released KGF or Lipoxin A4. f. Inhibit the apoptosis of epithelial/endothelial cells vis modulating hypoxia-induced factor-α and ROS. Downregulated cytokines and chemokines via MSC's also reduce hypoxia conditions and further help in the MSC's mediated process. g. MSC's inhibit the cell signaling pathways mediated by TLR or PRR's resultant in further modulation of cytokines and decreasing vascular permeability. h. Administered MSC's-CM or exosomes or MSC's also promote the process of angiogenesis via releasing several paracrine factors such as granulocyte-monocyte colony-stimulating factor, Interleukin-3, etc. i. Lung fibrosis also reduce via regenerating epithelial type II cells and by MSC's differentiated AT-II-like cells. The figure is made via biorender application: https://biorender.com/)

disease, both autologous, and the allogeneic infusion of MSCs are under clinical trial as depicted in Table 1 [61].

As of 1 October 2020, more than 60 clinical trials have been registered under the National Institute of Health (NIH) database, which are at different phases with different recruitment criteria. The dose of MSCs infusion majorly dependent on the body weight of patients in major clinical trials as depicted in Table 1, where the MSCs are administered intravenously. As per the current human clinical data, the MSCs are safe to infuse without generating adverse events or toxicity [58–60], although the efficacy of MSCs in treating various diseases still needs to be ascertained through further investigation with more number of patients [63–66]. The maximum follow up of patients is 6 months, while the inclusion and exclusion criteria of recruiting patients are from moderate-to-severe COVID 19 cases. The age group of patients lies in a range of 18 to 80 years with few exceptions to enrolling 10 years old and 90-year-old. The Infusion of autologous and allogenic infusion efficacy are poorly understood. The autologous infusion is considered safer, more effective, and elective option due to low or negligible risk of generating an immune response. In, contrast, during allogeneic infusion, sometimes the cells may undergo differentiation and altered HLA expression which may elicit the host immune response against infused MSCs marking them foreigners cells. Allogenic cells also tend to show less anti-inflammatory response because of similarity of host and donor cells [67]. Also, it has been proven in a meta-analysis study by McIntyre et al., in 2016 that allogenic MSCs show better outcomes compared to syngeneic and autologous counterparts [68] in treating acute lung injury. Nevertheless, keeping the fact in view that COVID-19 may be a life-threatening ailment and expanding the critically ill patient's MSC will be time-consuming, especially when they are not cryobanked previously, the use of allogenic MSCs is

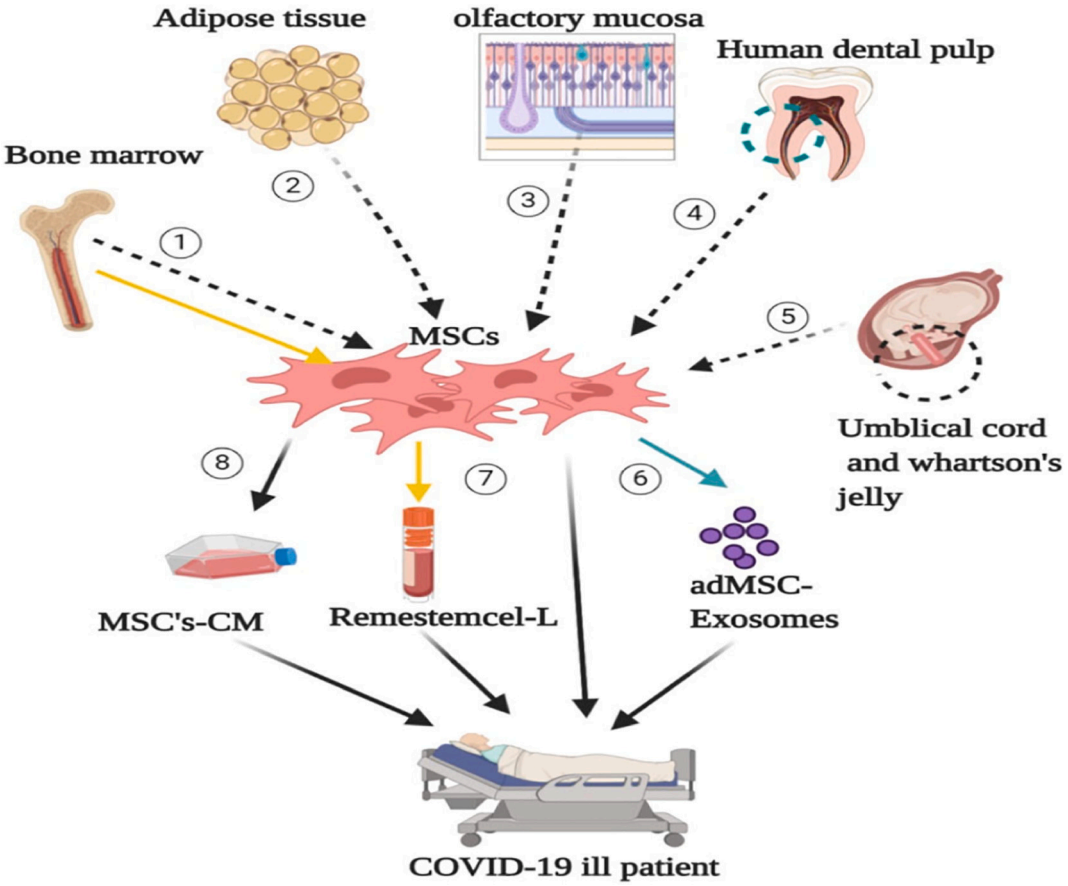

Fig. 4. Sources of Mesenchymal stem cells undergoing preclinical and clinical trials for the treatment of COVID-19: **1.** Bone marrow mesenchymal stem cells **2.** Adipose-derived mesenchymal stem cells **3.** Olfactory Mucosa derived mesenchymal stem cells **4.** Human dental pulp derived mesenchymal stem cells **5.** Umbilical cord and Wharton's jelly mesenchymal stem cells **6.** Adipose-derived mesenchymal stem cells secreted exosomes **7.** Remestemcel-L (Bone Marrow expanded and cryopreserved mesenchymal stem cells from an adult) **8.** Mesenchymal stem cells culture conditioned media The figure is made via biorender application: **https://biorender.com/**).

acceptable. Apart from bone marrow, cord blood, especially previously cryopreserved, contains both HSC as well MSCs can be a very good option for administration or transplantation and treating COVID-19 patients. Owing to safe administration in various clinical trials MSCs could be used for the ailment of COVID-19 until no breakthrough vaccine is availed publicly.

1.7. Clinical findings and trials of MSC in humans for COVID-19

Few pilot studies are present and published to elucidate MSCs role in treating COVID-19. In a pilot study conducted by Leng et al., 7 mild to severe type COVID-19 patients were enrolled and infused with 1×10^{6} MSCs cells/kg along with 3 placebo control patients. Clinical outcomes show no subsequent adverse effect and toxicity to infused MSC's. The underlying mechanism of MSCs to treat COVID-19 seems to be anti-inflammatory potential. Clinical efficacy outcomes of infused MSCs show decrease level of C-reaction protein, NK cells, T-cells, TNF-α, and increased the level of total lymphocyte, IL-10, IP-10 and vascular endothelial growth factor owing to repair damaged by COVID-19 virus [48].

In another study [69], clinical outcomes of a single patient were published reporting that the infused UC-MSCs are clinically effective and safe to administer. A 65-year old critically ill female was enrolled for the study and transfused with 5×10^{7} UC-MSCs cells intravenously at day 9 of infection with a further followed by two infusion with an interval of three days. After the infusion, the patient was shifted to the normal ward from ICU with a significant decreased in level of C-reaction protein, white blood, and neutrophil, ALT/AST along with increased level of total lymphocyte count. The study also suggested that the infusion of thymosin α1 will greatly enhance the immunomodulation potential of MSCs. A study conducted by commercial Pluristem therapeutics claimed 100% survival of patients treated with allogenic mesenchymal-like cells [70], while BioWorld commercial shows an 83% survival rate of ventilator-dependent COVID-19 patients when infused with mesoblast cells [71].

The primary data for safety and efficacy outcomes of MSCs infusion in mild to critical-ill COVID-19 patients shows MSCs as a promising candidate for combating the pandemic disease. However, the clinical outcomes are a result of a pilot study that recommends the enrolment of more patients and further investigation for the use of MSC as a therapeutic medicine for COVID-19.

2. Discussion

Nowadays, the exclusive subject, which is focused, discussed and evaluated is the ongoing pandemic of newly recognized COVID-19, which became a global public health emergency in just a few weeks and threatened mankind by disrupting the mental and physical well-being of people all across the globe. It is a well-known fact that COVID-19 majorly affects lungs resulting in inflammation, lung infiltration, fibrosis, and functional insufficiency of an immune response, acute respiratory distress syndrome via exacerbating the innate and adaptive response, which elevates the level of TNF-α, IFN-γ, IL-17, IL-4, colony-stimulating factor-M; G, IL-1β, IL-10, IL-7 and IL-12. [72] along with

Table 1
Clinical and preclinical trials of autologous allogenic MSC's and its derivative registered under https://clinicaltrials.gov for treatment of COVID-19.

CTRI no.	Source of MSC's	Recruitment/status	Phase/no. of participants	Treatment/intervention
NCT04313322	WJ-MSC's	Recruiting	1/5	Three IV doses of 1 × 10^6/kg WJ-MSC's will be injected intravenously COVID-19 diagnosed patient's
NCT04336254	hDPSC's	Recruiting	1/20	**Experimental group**: Routine treatment + Intravenous injection 3.0 × 10^7 hDPSC's solution of 30 ml on day 1, day 4 and administered on day 7 based on the treatment of COVID-19 **Control group:** Routine treatment + Intravenous administration of 3 ml of 0.9% saline
NCT04315987	NestCell®	Not yet recruiting	1/66	**Experimental group**: 2 × 10^7 cells on days 1, 3, and 5 in addition to standard care. If necessary, a dose will be given on day 7 **Control group:** Not specified
NCT04348435	HB-adMSCs	Enrolling by invitation	2/100	**Three experimental group**: Allogeneic HB-adMSCs 200MM,100MM,and 50MM at weeks 0,2,6,10 and 14 fives doses of Intravenous injection containing 20 x 10^7cells/dose,10 × 10^7cells/dose, and 5 x 10^7cells/dose will be administered respectively in each group **control group:** saline
NCT04366323	Allogenic-AdMSC's	Not yet recruiting	2/26	**Experimental group:** Two doses of 8 x 10^7cells/dose will be given **Control group:** Not specified
NCT04349631	HB-adMSCs	Enrolling by invitation	2/56	**Experimental group:** Five IV Intravenous injection of HB-adMSCs and inflammatory markers will be measured with baseline laboratory values accessed before the first infusion at weeks 6, 14, 26. SF-36 and PHQ-9 will be also accessed at week 2, 6, 10, 14, 18, 22, and 26. **Control group:** Not specified
NCT04252118	MSC's	Recruiting	1/20	**Experimental group:** Conventional treatment + three doses of 3 x 10^7cells/dose MSC's at day 0,3, and 6 **control group:** Conventional treatment
NCT04288102	MSC's	Recruiting	2/90	**Experimental group:** Conventional treatment + three doses of 3 x 10^7cells/dose MSC's at day 0,3, and 6 **control group:** Conventional treatment + three doses 1% HSA for the same period
NCT04273646	UC-MSC's	Not yet recruiting	NA/48	**Experimental group:** Conventional treatment + four doses of 0.5 × 10^6cells/kg MSC's at day 1,3,5, and 7 administered intravenously **control group:** Conventional treatment + four doses 1% HSA for the same time period
NCT04382547	Allogenic-OMdMSC's	Enrolling by invitation	1/40	**Experimental group:** Conventional treatment + Allogenic-OMdMSC's **control group:** Conventional treatment
NCT04346368	BM-MSC's	Not yet recruiting	1/20	**Experimental group:** Conventional treatment + single dose of 1 × 10^6cells/kg body weight of BM-MSC's at day 1 **control group:** Conventional treatment
NCT04302519	hDP-MSC's	Not yet recruiting	Early phase 1/ 24	**Experimental group:** Treatment with hDP-MSC's at day 1,3, and 7 **Control group:** Not specified
NCT04366063	MSC's and MSC's- EV's	Recruiting	2/20 of MSC's 3/20 of MSC's- EV's 20-control group	**Experimental group 1:** Conventional treatment + two doses of 10 × 10^7 MSC's/ doses of at day 0 and day 2 7 administered intravenously **Experimental group 2:** Experiment group 1 treatment + two doses of MSC's-EV's at day 4 and day 6 7 administered intravenously **control group:** Conventional treatment
NCT04339660	UC-MSC's	Recruiting	1/15 2/15	**Experimental group:** Conventional treatment + single dose of 100 ml suspended 1 × 10^6 UC-MSC's/kg body weight at day 1 if needed doses will be given again at an interval of 1 week. **control group:** Conventional treatment + 100 ml saline
NCT04392778	MSC's	Recruiting	1/30(10 each group)	**Experimental group 1:**patient's without a ventilator **Experimental group 2:** patient's on a ventilator saline injections **Experimental group 3:** patient's on a ventilator Three doses 3 × 10^7 MSC's/kg body weight at day 0,3, and 6 administered intravenously **Control group:** Not specified
NCT04371601	MSC's	Active, not recruiting	Early phase 1/60	**Experimental group:** Conventional treatment + four doses 106 MSC's/kg/time within 3 days of admission and then once every 4 days **3 control group:** active comparator 1.Oseltamivir drug treatment 2. Moderate amount of hormone treatment 3. Patients with oxygen therapy and other supportive therapies

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Table 1 (*continued*)

CTRI no.	Source of MSC's	Recruitment/status	Phase/no. of participants	Treatment/intervention
NCT04355728	UC-MSC's	Recruiting	1/24	**Experimental group:** Conventional treatment + two intravenous doses of 100 × 10^6 UC-MSC's/dose within 24 h. and 27 h. **control group:** conventional treatment
NCT04362189	HB-adMSCs	Not yet recruiting	2/100	**Experimental group**: Four doses of Allogeneic 10 x 10^7cells/dose HB-adMSCs administrated intravenously at day 0,3,7,10 and 14 **control group:** saline
NCT04390152	WJ-MSC's	Not yet recruiting	1/40	**Experimental group**: Standard treatment therapy with drugs (400 mg Hydroxychloroquine + Lopinavir/ Ritonavir 400/100 or azithromycin 500 mg) + two doses of 5 × 10^7 WJ-MSC's /dose administrated intravenously **control group:** standard therapy + saline
NCT04348461	Allogenic and expanded-adMSC	Not yet recruiting	2/100	**Experimental group**: Standard treatment therapy + two doses of 1.5 × 10^6 adMSC's /kg administrated intravenously **control group:** standard therapy
NCT04331613	CAstem	Recruiting	2/9	**Experimental 3 cohort group**: doses of 3 × 10^6, 5 × 10^6, and 10 × 10^6 CAstem in each respective group **Control group:** Not specified
NCT04377334	Allogenic BM-MSC's	Not yet recruiting	2/40	**Experimental group**: Infusion of Allogenic BM-MSC's
NCT04390139	WJ-MSC's	Recruiting	1/30	**Experimental group**: Standard treatment therapy + two doses of 1 × 10^6 WJ-MSC's /kg administrated intravenously at day 1 and day 3 **control group:** standard therapy + saline
NCT04400032	BM-MSC's	Not yet recruiting	1/9	**Experimental 3 cohort group**: doses of 25 × 10^6, 50 × 10^6, and 90 × 10^6 BM-MSC's administered in each respective group for 3 consecutive days
NCT04398303	ACT-20-MSC ACT-20-CM	Not yet recruiting	1/10(5 moderate ill + 5 severe COVID-19)	**Experimental group 1**: Standard treatment therapy + intravenous administration of 1 × 10^6 ACT-20-MSC in 100 ml of ACT-20-CM **Experimental group 2**: Standard treatment therapy + intravenous administration of 1 × 10^6 ACT-20-CM
			2/30(15 moderate ill + 15 severe COVID-19)	**Experimental group 1**: Standard treatment therapy + intravenous administration of 1 × 10^6 ACT-20-MSC in 100 ml of ACT-20-CM **Experimental group 2**: Standard treatment therapy + intravenous administration of 1 × 10^6 ACT-20-CM **Control group:** Standard treatment therapy + 100 ml of αMEM
NCT04397796	Allogenic-BM-MSC's	Not yet recruiting	1/45	**Experimental group 2**: Infusion of Allogenic-BM-MSC's **Control group:** Plasmalyte and HSA
NCT04371393	Remestemcel-L (MSC's)	Recruiting	3/300	**Experimental group 1**: Standard care + two doses of 2 × 10^6 Remestemcel-L/kg of body weight for 1 week administrated intravenously **Control group:** Standard treatment care + plasma-Lyte
NCT03042143	UC- CD362 + MSC's	Recruiting	2/75	**Experimental group 1**: 40 × 10^6 UC- CD362 + MSC's administrated for 30–90 min **Control group:** Infusion of Plasmalyte 180 for 30–90 min
NCT04345601	Mesenchymal stromal cells	Not yet recruiting	Early phase1/30	**Experimental group 1**: A single dose of 1 × 10^8 Mesenchymal stromal cells administrated intravenously **Control group:** Not specified
NCT04269525	UC-MSC's	Recruiting	2/10	**Experimental group 1**: A single dose of 3.3 × 10^7 UC-MSC's/50 ml/bag Mesenchymal stromal cells administrated intravenously 3bags each time at day 1, 3,5 and 7 **Control group:** Not specified
NCT04361942	Mesenchymal stromal cells	Recruiting	2/24	**Experimental group 1**: A single dose of 1 × 10^6 Mesenchymal stromal cells/kg in diluted 100 ml saline administrated intravenously **Control group:** Infusion of 100 ml of saline
NCT04333368	WJ-MSC's	Recruiting	2/40	**Experimental group 1**: Three doses of 1 × 10^6 WJ-MSC's administered via central venous route at day 1, day 3, day 5 **Control group:** Infusion of 150 ml of 0.9% NaCl

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Table 1 (*continued*)

CTRI no.	Source of MSC's	Recruitment/status	Phase/no. of participants	Treatment/intervention
NCT04389450	PLX-PAD (MSC's)	Not yet recruiting	2/140	**Experimental group 1**: Two doses of PLX-PAD administered intramuscularly with a gap of one week **Experimental group 2**: One dose of PLX-PAD administered intramuscularly and one placebo dose at the same time interval **Control group for 1 & 2:** Two dose of placebo for the same time interval **Experimental group 3:** A single dose of PLX-PAD administered intramuscularly **Control group for 3:** One dose of placebo
NCT04367077	Multistem	Recruiting	2/400	**Experimental group 1**: Infusion of multistem **Control group:** Infusion of saline
NCT04276987	MSC's derived exosomes	Not yet recruiting	1/30	**Experimental group 1**: 2×10^8 nanovesicles/3 ml aerosol inhalation of MSC's derived exosomes at day 1, day 2, day 3, day4, day5
NCT04444271	BM-MSC's	Recruiting	2/20	**Experimental group 1**: 2×10^6 BM-MSC's cells/kg in diluted 100 ml saline administrated intravenously at day 1 and day 7(if required) + standard care **Control group:** Infusion of saline
NCT04416139	Allogenic-MSC's	Recruiting	2/10	**Experimental group 1**: A single dose of 1×10^6 MSC's cells/kg administrated intravenously
NCT04456361	WJ-MSC's	Active, Not recruiting	1/9	**Experimental group 1**: A single dose of 1×10^8 MSC's cells/kg administrated intravenously
NCT04452097	UC-MSC's	Not yet recruiting	1/9	**Experimental group 1**: Standard treatment therapy + intravenous administration of 0.5×10^6 kg/ of body weight UC-MSC's **Experimental group 2**: Standard treatment therapy + intravenous administration of 1×10^6 kg/ of body weight UC-MSC's **Experimental group 3**: Standard treatment therapy + intravenous administration of 1.5×10^6 kg/ of body weight UC-MSC's
NCT04429763	UC-MSC's	Not yet recruiting	2/30	**Experimental group 1**: 1×10^6 UC-MSC's cells/kg + standard care treatment **Control group:** Infusion of saline
NCT04428801	AdMSC's	Not yet recruiting	2/200	**Experimental group 1**: Three doses 200×10^6 Ad-MSC's cells intravenously administration in alternate three days **Control group:** Infusion of placebo doses
NCT04352803	AdMSC's	Not yet recruiting	1/20	**Experimental group 1**: intravenous administration of 5×10^5 Ad-MSC's cells/kg + conventional treatment **Control group:** conventional treatment

WJ-MSC's: Wharton jelly Mesenchymal stem cells, hDPSC's: human Dental Pulp derived Mesenchymal stem cells, HBadMSCs: Hope Biosciences adipose derived Mesenchymal stem cells, Health Survey (SF-36), depression module (PHQ-9), HSA: Human serum albumin, UC-MSC's: Umbilical Cord Mesenchymal stem cells, OMdMSC's: Olfactory Mucosa-derived Mesenchymal Stem Cells, BM-MSC's: Bone Marrow-derived Mesenchymal Stem Cells (BM-MSCs), EV's: Extracellular vesicles, ACT-20-MSC:allogenic human Umbilical derived Mesenchymal Stem Cells, ACT-20-CM: Allogenic human Umbilical derived Mesenchymal Stem Cells in Conditioned Media, α-MEM: Minimal Essential Media, PLX-PAD: allogeneic ex vivo expanded Placental Mesenchymal-like adherent Stromal Cells

chemokines elevation, such as MCP-1 or CCL-2, MIP-1A interferon gamma-induced protein 10 or CXCL-10 [73]. Owing to excessive infectivity and mortality rates, the prime interest of the worldwide clinical and scientific community today is to combat and manage the COVID-19 pandemic with the utmost priority. There are numerous antiviral drugs and their combinations under clinical trials, but to date, neither any prominent candidate for targeted drug nor any vaccine has been discovered hitherto, which leads to the inevitabilities of disease treatment by other means. Stem cells owing to the potential of self-renewal and differentiation could be used as a better alternative for the treatment and management of this disease outbreak. Among stem cells, MSCs may have an upper hand, based-on the immune-modulatory, homing, anti-inflammatory and regenerative potential, that is already proven in various diseases such as SARS-CoV, Pneumonia, ALI, ARDS, COPD, GvHD [74,75]. The regenerative potential of MSCs is still controversial as they may fail to differentiate themselves after infusion. However, they may elicit regenerative potential by signaling the naïve stem cells of the host body [33,56].

With scarce therapeutic options, MSCs could act as a forefront treatment for the counterattack of SARS-CoV-2 virus, as these cells (i) Repairs the damage pulmonary epithelial cells via regenerative potential (ii) Differentiate into type II alveolar epithelial-like cells [53], which gets damaged as a result of hyperimmune response started with SARS-CoV -2 infection (iii) Lack the expression of ACE-2 receptor and TMPRSS2 protease, which have been proven crucial for viral entry in host cells, thus, eliminating the risk of susceptibility to COVID-19 infection [48]. (iv)Induction of allogeneic tolerance (v) Reduction in pulmonary edema via lipoxin A4 [76]. (vi) Bacterial clearance via the release of an antibacterial peptide [77]. (vii) Reduced alveolar epithelial and arterial endothelial cell apoptosis via modulating signaling of hypoxia-inducible factor (HIF-α) and reactive oxygen species resulting in inhibition of caspase-3 mediated apoptosis [78].

3. Conclusion

As discussed in our review and suggested by numerous scientists, autologous and allogeneic infusion of MSCs, which are primarily ACE 2 negative, henceforth resistant to SARS-CoV-2, could be an ideal solution for treating a disease which can be used alone or as a combination with antiviral drugs. MSCs potential as a COVID-19 treatment is still in the initial phase of implementation and testing by researchers in plenty of preclinical and clinical trials. Although initial experimental clinical

trials with limited and preliminary data are unable to provide any assertive recommendations regarding the disease severity or mortality and require further trials and follow-ups. The safety and efficacy of MSCs administration in terms of source, source preparation for infusion, autologous or allogenic nature, adequate dose, route of MSC delivery, and timing of MSC delivery are also under trial. The ideal candidate among COVID -19 patients for MSC therapy seems to the one who are showing advanced symptoms of disease, Proceeding towards ARDS and are already on antiviral drug treatment. Moreover, the results of ongoing trials will clarify the eligibility of ideal patients for MSC transplants along with the depiction of risk factors and the safety of individuals already on ventilator support. To date, no clinical trials have been completed, even though various clinical trials are underway thus the exact outcome and complete implementation of MSCs as a therapeutic agent seems to take a while.

Apart from promising preliminary data of MSCs as a potential candidate for treating the COVID-19, clinical implementation of stem cells as a therapeutics is cost-effective and always a matter of controversy due to its ethical issues involved, incomplete data of MSCs processing, screening of patients, follow-up and efficacy. However, in light of the current pandemic scenarios and lack of unanimous point-of-care therapy for the SARS-CoV-2, it is worthwhile to give a chance to stem cells for the treatment of this deadly disease. Irrespective of current treatment and therapeutic approach researchers from worldwide are working in harmony to develop a potential vaccine to combat COVID-19 disease.

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Consent for publication

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Availability of data and materials

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Authors' contributions

PY collected literature, drafted, designed, wrote, and edited the manuscript. RV revised and edited the manuscript. AB edited and improvised the manuscript. RB conceptualized the outline and topic of the article, edited and prepared the manuscript for submission. All authors read and approved the final manuscript. All authors read and approve the manuscript for submission.

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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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