ISSN 2449-8955 European Journal of Biological Research *Review Article*

DOI: http://dx.doi.org/10.5281/zenodo.5813126

Anti-fibrotic agents could be the game-changer for post-COVID-19 pulmonary fibrosis treatment

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Received: 07 September 2021; **Revised submission:** 23 November 2021; **Accepted:** 16 December 2021

https://jbrodka.com/index.php/ejbr

ABSTRACT: More than 220 countries and territories are globally affected by the recent pandemic COVID-19 which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). There is possibility of third wave of this pandemic as per epidemiological and public health experts. Besides that post-COVID-19 complications are alarming matter to look upon. Post-COVID-19 complications include several symptoms like as persistent fever; cough; fatigue; headache; attention disorder; dyspnea; anosmia; ageusia; chest pain discomfort; various respiratory illness; acute respiratory distress syndrome (ARDS) etc., and here the things to worry about is the development of pulmonary fibrosis after COVID-19. In some COVID-19 patients, hyper-inflammation in the form of 'cytokine storm' along with dysregulated immune response, alveolar epithelial tissue injury and wound repair collectively cause this secondary pulmonary fibrosis. Therefore, using anti-fibrotic agents e.g. pirfenidone, nintedanib and other natural compounds could be meaningful in these circumstances although their efficacy in treating COVID-19 is subject to more detailed laboratory research works. In this review article, we have discussed the progression of pulmonary fibrosis development which is triggered by COVID-19; probable solutions with anti-fibrotic agents including anti-fibrotic drugs, some well-known natural compounds, combined anti-fibrotic therapies; and the current challenges of this field.

Keywords: COVID-19; Post-COVID-19 pulmonary fibrosis; Lung injury; Anti-fibrotic agents.

Abbreviations:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), acute respiratory distress syndrome (ARDS), Middle East Respiratory Syndrome (MERS), severe acute respiratory syndrome (SARS), ORF (open reading frame), dipeptidyl peptidase 4 (DPP4), angiotensin-converting enzyme 2 (ACE2), transforming growth factor-beta 1 (TGF-β1), angiotensinogen (AGT), connective tissue growth factor (CTGF), vascular endothelial growth factor (VEGF), fibronectin (FN), interleukin-6 (IL-6), 3C-like protease (3CLpro), RNA-dependent RNA polymerase (RdRp), papain-like cysteine protease (PLpro), idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD), Mesenchymal Stem Cells (MSCs), Galectin-3 (gal-3), Hepatocyte growth factor (HGF).

1. INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which is earlier known as 2019 novel coronavirus (2019-nCoV) causes COVID-19 viral disease globally and till now affected more or less 220 countries [1–3]. Due to this outbreak and pandemic situation as of August 22, 2021, 07:08 GMT, 212,172,598 cases and 4,437,019 deaths reported globally and in India the active cases is 353,366, and total death number is 434,399. The current cases distribution of COVID-19 is represented here in Fig. 1 [4,5].

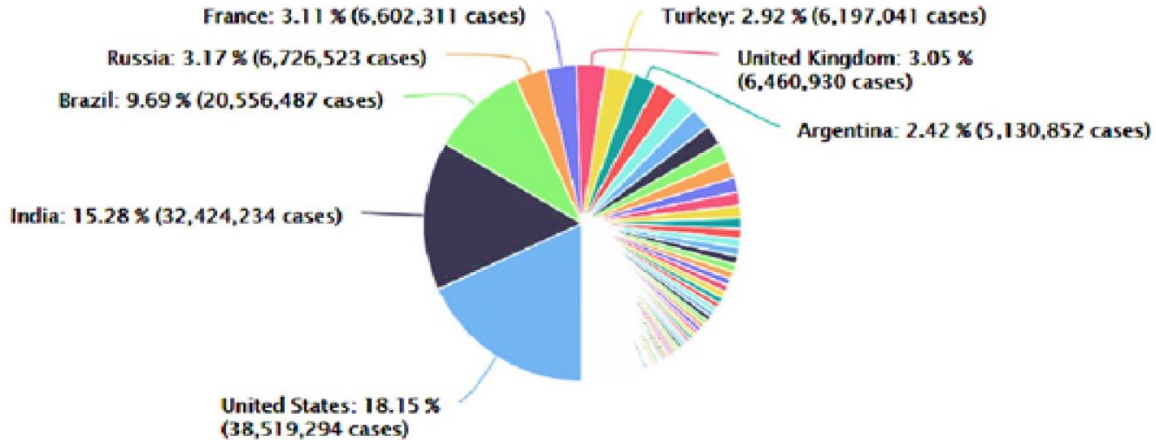

Figure 1. Countries cases distribution of COVID-19 infection as of August 22, 2021, 07:08 GMT. This figure represents the total case distribution of different countries during COVID-19 pandemic second wave [4].

But in India as of 22nd August 2021, 25,420 new cases and 385 new deaths are reported which is a little less than it was during the second wave [4], therefore, it seems to us that the situation now in India is somewhat under control but according to various epidemiologists, scientists, clinicians world-wide there is possibility of third wave which may knock the door if we ignore to take proper safety measures along with vaccination.

Ortho-coronavirinae is the subfamily of this virus where the Alpha, Beta, Gamma and Delta coronavirus are four genera of this subfamily and other three [6,7] are Middle East Respiratory Syndrome (MERS), severe acute respiratory syndrome (SARS) and finally SARS-CoV-2 responsible for the pandemic COVID-19 [1,8]. The alphacoronavirus and betacoronaviruses known to infect mammals but others are generally avian pathogens named as gammacoronavirus and deltacoronaviruses [9]. HCoV-NL63 and HCoV-229E belong to alpha genera, while the other four including MERS, HCoV-OC43, HCoV-HKU1, SARS-CoV (or SARS-CoV-1) are form beta genera. The beta coronavirus genus further divided into several subgenera Embecovirus, Hibecovirus, Merbecovirus, Nobecovirus and Sarbecovirus MERS-CoV [10].

In December 2019, this virus first reported in Wuhan City, Hubei Province, Central China, that causing some common symptoms like fever, dry cough and fatigue on the other some severe symptoms like as respiratory illnesses, shortness of breath, loss of appetite, persistent pain or pressure in the chest, high temperature (above 38°C) and persistent fever, dysgeusia, lung injury, acute respiratory distress syndrome (ARDS) with epithelial and endothelial injury in some individuals [11–13]. It is reported that among the seventh members, four result in minor symptoms related to the upper respiratory tract. On the other hand, the rest three including SARS-CoV-2 cause lower respiratory tract infections that's leads to major lung complications such as acute respiratory distress syndrome (ARDS), cytokine release syndrome and pulmonary

fibrosis (PF) which starts early in the course of ARDS as PF is a recognized sequel of ARDS [10,13]. The most dangerous consequences of this viral infection that was already hypothesized [15,16] is found to be real in the current scenario as of chest physicians from all over the world recognized peoples recovered from COVID-19 still left with lung fibrosis that is termed here as post-COVID-19 lung fibrosis [14,17]. This view is also supported by Lopez-Leon et al., in their very recent study and have recognized PF as one of the post-COVID-19 complications [18]. It has been suggested that the pulmonary fibrosis is interconnected to the pathology of ARDS, that's has three phases: exudative, proliferative, and fibrotic, where in the first week or you can say at initial stage, the diffuse alveolar damage, the exudative phase with edema, hyaline membranes, and interstitial acute inflammation occurs and next to that an organizing phase with loose organizing fibrosis and fibro-proliferative phase and, in non-survivors, end-stage fibrotic lung can be seen [12,14,17,19].

In COVID-19 disease, the various pro-inflammatory cytokines are produced abnormally in higher level along with excessive infiltration of inflammatory cells, the phenomenon is also known as 'cytokine strom', which is believed to be key event in COVID-19 mortality and morbidity and due to this abnormal inflammatory event, the pulmonary fibrosis can be promoted [14,20]. Reported data also supports the view that about 40% of patients with COVID-19 develop ARDS, and 20% experienced more severity and may further leads to fibrosis later [14,19]. For this reason using anti-fibrotic therapies could be a game changer in this situation and some of the approved anti-fibrotic drugs for e.g. pirfenidone and nintedanib [21,22] which are effective against lung functional abnormalities and improving life can be administrated. Here in this article, we will discuss about the post-COVID-19 lung fibrosis and how this lung fibrosis gets developed and disrupted by COVID-19 virus. After that we have discussed about some potential anti-fibrotic agents that could be used as potential therapeutics for post-COVID-19 pulmonary fibrotic patients depending on other co-morbidities and severity of the disease.

2. CORONAVIRUS DISEASE 2019 (COVID-19) PATHOLOGY

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a RNA virus and its genome size is 30 kb, that's mainly code for several proteins (poly proteins)also known as ORF1a/b (open reading frame) and it furthers cleaved into more several proteins parts among them, 5 accessory and 4 structural proteins important for its assembly and infectiveness including spike surface glycoprotein, membrane protein, envelop protein and neucleocapsid [1,23,24]. It is the seventh member from the family that infect humans with approximately 70% genetic similarity to SARS-CoV and the site of infection is mainly depends upon the presence of the dipeptidyl peptidase 4 (DPP4) and angiotensin-converting enzyme 2 (ACE2), where the viral spike protein binds also similar for MERS and SARS [1,11,25–27]. As most of the human cells related to lower respiratory tract including endothelial, alveolar cells, further tracheal, bronchial cells bearing the ACE2 receptor, the SARS-CoV-2 virus which has 10-20 fold greater affinity towards this than SARS-CoV easily in a faster way enters and upon replicating inside host cells initiates the immune-pathogenesis and resulting huge amount of local cytokines secretion causing lung tissue damages, acute respiratory distress syndrome (ARDS), multiple organ failure [1,28,29]. Decreased immune functions, reduction of lymphocytic T Cells (CD4+ and CD8+) and natural killer (NK) cells and the high level of inflammatory cytokines (IL-2, IL-6, IL-7, IL-10), MCP-1, MIP-1α and TNF-α are linked with SARS-CoV-2 severity [30,31]. Most susceptible groups for this viral infection are older people but in the second wave, in India 18+ young generations are included in this range, even kids (below the age of 16) are right now and may be in the next wave prone to the dangers [32].

3. PULMONARY FIBROSIS AFTER COVID-19

Several data available from autopsy, clinical radiography have shown that the novel corona virus damages mainly the respiratory system and in the long run its causes pulmonary fibrosis [11,12,14,19]. We know very well about the pathogenic mechanism of viral lung fibrosis, as it has been studied with others viruses like influenza and SARS, where it has been reported that, in case of H1N1 influenza the transforming growth factor-beta 1 (TGF-β1) level increased, found similar for SARS-CoV-1 (outbreak in 2002) and due to higher level of this cytokine the extracellular matrix proteins deposition and fibroblast differentiations takes place in abnormal manners that finally promote the lung fibrosis [17,33,34]. In case of novel corona virus, the molecular mechanism for the progression of pulmonary fibrosis is not clearly understood but believed to depends upon various factors and similar to SARS-CoV [14].

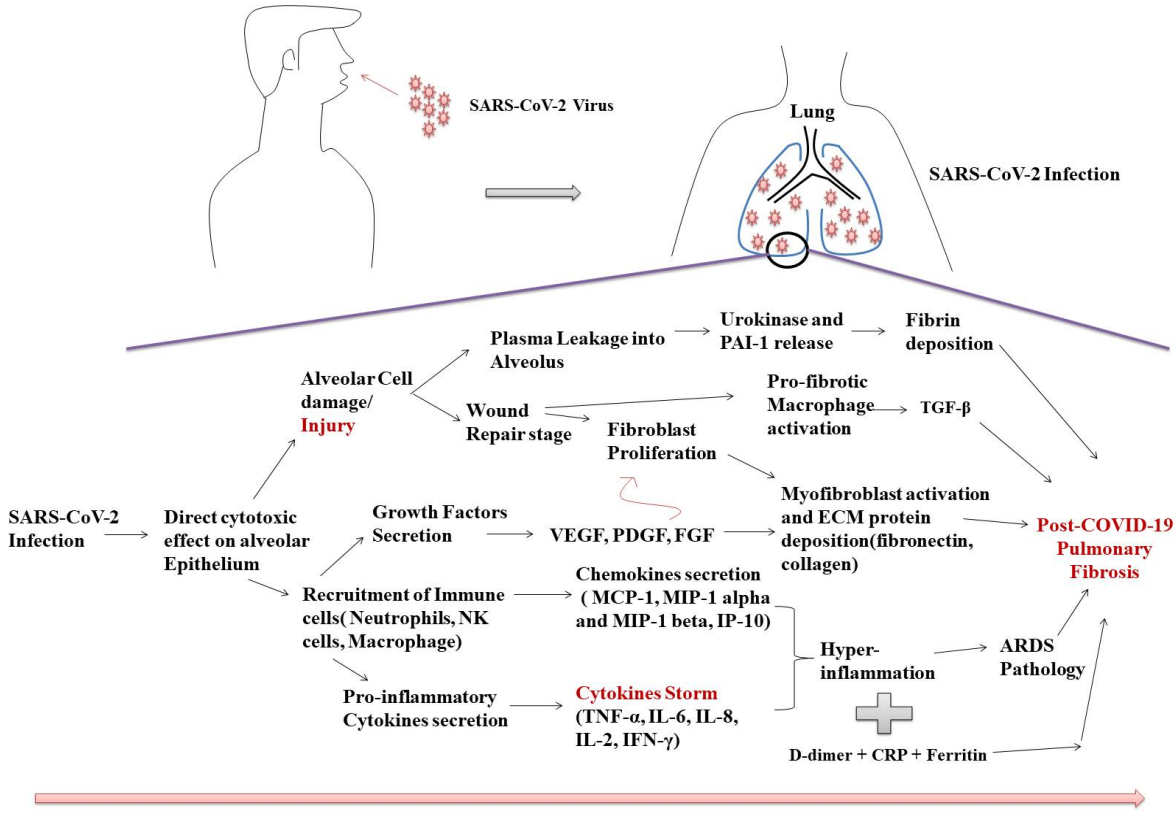

Figure 2. General pathway of pulmonary fibrosis development triggered by COVID-19 infection.

The SARS-CoV-2 virus upon infection causes alveolar cell damage that activates immune cells like neutrophils, macrophages and natural killer cells (NK cells). Then they start to secrete various pro-inflammatory cytokines including tumor necrosis factor-alpha (TNF-alpha), interleukins (IL)-6, IL-8, IL-2 and interferon (IFN)-gamma. These causes cytokine storm and promote hyper inflammation and ARDS pathology. On the other hand due to tissue injury and wound repairing, there are release of some growth factors like VEGF, FGF, PDGF which cause fibroblast proliferation and transformation to myofibroblast with extracellular matrix protein deposition. The plasma leakage also causes fibrin deposition. TGF-β, the pro-fibrotic cytokine is released from pro-fibrotic macrophage. Cytokine storm (hyperinflammation), ARDS pathology, ECM proteins deposition all together with other factors (D-dimer, ferritin and C-reactive protein) as shown in this schematic finally contribute in the development of post-COVID-19 pulmonary fibrosis.

A very recent research by Xu et al., [35] confirmed that SARS-CoV-2 binds to the ACE2 cause activation of fibrosis related process and genes, like as altered expression in mRNA and protein level of angiotensinogen (AGT), transformation growth factor-beta 1 (TGF-β1), connective tissue growth factor (CTGF), vascular endothelial growth factor (VEGF) and fibronectin (FN), are observed by the bioinformatics studies which are also found in the patients with lung fibrosis [29]. So here in SARS-CoV-2, it may be also possible that its first activates the TGF-β pathway then through this signaling its increased the ECM proteins mainly the FN and the thus the alveolar-epithelial cells may result in lung fibrosis [17,35]. In addition to this, decreasing of ACE-2 level causes up-regulation of angiotensin 2, which plays key role in the development of inflammation and fibrosis by generation of reactive oxygen species (ROS), production of the pro-inflammatory cytokines mainly interleukin-6 (IL-6) and IL-8 and activation of TGF-β signaling is also postulated [17,36]. Furthermore, It is also possible that oxygen toxicity (oxygen-derived free radicals) and mechanical stress or ventilation (including barotrauma and volutrauma) can cause lung and pulmonary injury, contributing to ARDS in which during inflammatory stage matrix metallo-protease released in abnormal manners and causes endothelial injury, increase cytokine production, upsurge epithelial-mesenchymal transition (EMT) and collagen deposition in lung and finally all these contributing to pulmonary fibrosis [16,35–37]. From several scientific reports, medical observations and evidences we can summarize that after SARS-CoV-2 infection in some patients, activation of the TGF-β signaling; inflammation (cytokine storm); ARDS pathology the well-known acute and diffuse inflammatory damage into the alveolar-capillary barrier; high ROS level; accumulation and deposition of ECM proteins all are involved for the post-COVID-19 pulmonary fibrosis generation. There may be more unknown pathways, signaling crosstalk's which are directly or indirectly causes lung fibrosis are yet to discover and gradually will be published through research in upcoming days.

4. ANTI-FIBROTICS, THE GAME CHANGERS

Based on current scenario, using anti-fibrotic drugs are may be very useful to tackle the post-COVID-19 pulmonary fibrosis [12,19,40]. There are some well-known chemical compounds such as pirfenidone and nintedanib (FDA-approved) and some natural compounds including quercetin, baicalin and baicalein, and salvianolic acid B are recognized as potential anti-fibrotic agents that can be applied to the COVID-19 patients to save them from the development of pulmonary fibrosis and other consequences.

Pirfenidone is an oral drug that has anti-fibrotic, anti-oxidative and anti-inflammatory properties on the other, nintedanib is also an good anti-fibrotic agents that's being an tyrosine kinase inhibitor regulate downstream signaling of fibrosis, it also has anti-inflammatory property and inhibits IL-6 and IL-1 [12,40,41]. Others well-known natural compounds that exhibit anti-fibrotic effects are some flavonoids and non-flavonoids. From fruits and vegetables we have the quercetin which shows dose dependent anti-fibrotic activity *in vitro* [42]. Recent *in silico* and *in vitro* studies suggested that quercetin can performed key role to modulate various stages of the coronavirus entry into host cells and also with replication cycle [42,43]. Previous studies with viral 3C-like protease (3CLpro) of SARS-CoV and with others important targets parts of SARS-CoV-2 like the host entry apparatus, spike protein and ACE2 receptor, the RNA-dependent RNA polymerase (RdRp), that is crucial for the replication of viral RNA, and papain-like cysteine protease (PLpro), that's controlling virus maturation, impairment of host inflammation, suggested that the quercetin binds better with all these [44]. Furthermore, The baicalin and baicalein also can be acts as novel inhibitors of SARS-CoV-2 3CL protease [45]. The salvianolic acid B that's is available in *Salvia miltiorrhiza*, it is also

found effective to inhibit the entry of 2019-nCoV spike pseudovirus into angiotensin-converting enzyme 2 high-expressing HEK293T cells (ACE2h) cells by binding to the RBD of the 2019-nCoV spike protein and ACE2 protein [42,46]. The full list of these chemical and herbal compounds and their key functions including antiviral role summarized in the Table 1.

Table 1. Brief details about some well-known anti-fibrotic drugs (some of the potential anti-fibrotic and there antiviral property are briefly presented here in this table).

Drugs/ Compounds	Key function	Antiviral activity	References
Pirfenidone	It has anti-fibrotic, anti-inflammatory, anti-oxidative, inhibits IL-6 and IL-1	Not reported	[12,40]
Nintedanib	It inhibits downstream molecules involved in fibrosis, control fibroblast differentiations	Not reported	[12,40,41]
Quercetin	*In vitro* study found dose-dependent anti-fibrotic activity and low cytotoxicity	Anti-COVID-19 activity by modulating its entry into host cells and also with replication cycle	[42,43]
Baicalin and Baicalein	It has both anti-inflammation and anti-fibrosis activity	Antiviral property against influenza and dengue virus also anti COVID-19 activity	[43,45-47]
Salvianolic acid B	Major functions are anti-fibrosis and it suppressed TGF-β1	Anti-COVID-19 activity by inhibiting the entry of 2019-nCoV spike pseudovirus into ACE2 cells	[42,46]

5. DISCUSSION

Now we have some ideas regarding development and progression of fibrosis in lungs of some COVID-19 patients and how the pathology of lung injury gets modulated by the COVID-19 viral infection. In this article we have summarized some potent anti-fibrotic agents both chemical and herbal that could be used for better treatment. Upon analysis the data represented here in table 1 and through literature's review [41,42,44–47], we have found that natural compounds including quercetin, baicalin and baicalein, and salvianolic acid B could be serve as most potential agents for the treatment of post-COVID lung fibrosis as they possess both antiviral and anti-fibrotic properties. Thus using anti-fibrotic agents could be the game changer. According to George PM et al., [12,17] using the anti-fibrotics can be considered within the first week of ARDS onset but their efficacy in treating COVID-19 is subject to more detailed laboratory research. The anti-fibrotic agents also have some pleiotropic effects so how to tackle this problem should be our prior concerns. A randomized, open clinical trial to evaluate the efficacy and safety of pirfenidone (ClinicalTrials.gov identifier: NCT04282902) is currently going on and in its phase 3 and more longer follow-up durations are mandatory to get better inference [15]. Recently it is reported that nintedanib can be used as an adjunct treatment for patients suffering from post-COVID-19 pulmonary fibrosis because it can result betterment of lung function [48]. Another clinical trial is going on to evaluate the impact of colchicine on post-COVID-19 pulmonary fibrosis and the trial is in phase 4 at present (ClinicalTrials.gov identifier: NCT04818489) [49]. For the natural compounds the low bioavailability and lacking of proper dose standardization is a limitation. Instead of these we can think of using them for better treatment purpose in this emergency situation.

Apart from these anti-fibrotic approaches several other therapeutic strategies may be useful in this field. A group of researchers [50] performed bioinformatics studies where they found that the idiopathic pulmonary fibrosis (IPF), chronic obstructive pulmonary disease (COPD) patients are subject to high risk to be infected by SARS-CoV-2. The transcriptomic analysis also revealed similar pathways and identified some genes which are responsible for diffident types of respiratory diseases like IPF and COPD, so that could be

used for better therapeutic targets [50]. Very recent a report from a case study at Japan expressed that treatment with high-dose steroids including pulse steroid therapy is found to be beneficial for patients suffering from acute exacerbations of IPF triggered by COVID-19 [51].

On the other, using Mesenchymal Stem Cells (MSCs) as therapeutics also could be a very important approach that has been reviewed by Vishnupriya et al. [11]. The MSCs, reached the site of injury and inhibits the inflammations, its secretes some factors like hepatocyte growth factor (HGF), which disturbed the TGF-β signaling and prevent tissue fibrosis [11]. The galectin-3 (gal-3) that's a carbohydrate binding protein expressed by the macrophages and alveolar epithelial cells of lung and found to be related with the abnormal inflammation known as 'cytokine strom' and lung fibrosis so using inhibitors for them could also be a good therapeutic approach that has been reviewed by Garcia-Revilla et al. [20]. Recent study by McGroder et al., suggested that age-adjusted telomere length should be considered as an independent risk factor for post-COVID-19 pulmonary fibrosis [52]. Proper identification of risk factors and biomarkers for earlier stage of lung fibrosis is very crucial to diagnose which of these patients will proceed to develop fibrosis and so that we can implement specific therapeutics.

Although, for now it is still a big question that why only some individuals develop this post-COVID-19 pulmonary fibrosis and others recovers from it. Probably there are involvements of some other risk factors such as co-morbidities, age, severity of initial illness, and duration of mechanical ventilation, several genetic or epigenetic factors which are also a subject of research. There are some other obvious questions are needed to be addressed in future like: a) What are the different signaling pathways involved to the progression of post-COVID-19 pulmonary fibrosis development; b) Can we use the anti-fibrotic drugs as a combinational therapy with others anti-viral and anti-inflammatory drugs; c) What will be the efficacy of anti-fibrotic drugs within vaccinated and non-vaccinated persons; and also among peoples who have other co-morbidities; d) What is the underlying mechanism for activation of TGF-β signaling which is regulated by SARS-CoV-2 in some COVID-19 patients or is there involvement of any other signaling cross-talk.

6. CONCLUSION

Finally after considering all the above-mentioned points, now we can say that it will be very meaningful to use the anti-fibrotic drugs against post-COVID-19 pulmonary fibrosis in future. Although more understanding of pathophysiology of this lung fibrosis is required for better inference. In case of personalized gene based treatment, more knowledge about the confirmed risk factors responsible is required. In this situation detailed laboratory work to be performed to fill the gaps.

Authors' Contributions: The research idea came from KC. PC did literature review, prepared the manuscript and performed referencing under the supervision of KC. KC critically revised the work. Both authors read and approved the final manuscript.

Conflict of Interest: The authors declare no conflict of interest.

Funding: Not applicable.

Declaration: Information's presented here after giving proper credits to the original authors or source. We further make no representations that the data available in the referenced papers is free from error. We apologize if we missed to cite your valuable paper due to place issue. The graphical representation (Fig. 1) is collected from the Worldometer www.worldometers.info.

REFERENCES

1. Li H, Liu S, Yu X, Tang S, Tang C. Coronavirus disease 2019 (COVID-19): current status and future perspectives. Int J Antimicrob Agents. 2020; 5: 105951.
2. Xu X, Chen P, Wang J, Feng J, Zhou H, Li X, et al. Evolution of the novel coronavirus from the ongoing Wuhan outbreak and modeling of its spike protein for risk of human transmission. Sci China Life Sci. 2020; 63: 457–460.
3. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. 2020; 5: 536–544.
4. Coronavirus data. Available from: (https://www.worldometers.info/coronavirus/coronavirus-death-rate/) [Cited 2021 August].
5. COVID-19_pandemic_data. Available from: https://en.wikipedia.org/wiki Template: COVID-19_pandemic_data [Cited 2021 August].
6. Chakraborty K. COVID-19: Zoonotic Origin, Interspecies Transmission, Virus-Host Interaction and Animals Susceptibility to SARS-CoV-2. EC Pulmonol Respir Med. 2020; 9: 52-60.
7. Coronavirus types. Available from: https://www.cdc.gov/coronavirus/types.html. [Cited May 2021]
8. Banerjee A, Kulcsar K, Misra V, Frieman M MK. Bats and coronaviruses. Viruses. 2019. 11: p41.
9. Mitra A. Investigations into the origin of SARS-CoV-2: an update. Curr Sci. 2021; 121: 77–84.
10. What Is Orthocoronavirinae? Available from: (https://www.latestly.com/lifestyle/health-wellness/what-is-orthocoronavirinae-know-the-meaning-origin-and-sections-of-the-subfamily-the-novel-coronavirus-is-a-part-of-1826507.html) [Cited 2021 November].
11. Vishnupriya M, Naveenkumar M, Manjima K, Sooryasree NV, Saranya T, Ramya S, et al. Post-COVID pulmonary fibrosis: Therapeutic efficacy using with mesenchymal stem cells – How the lung heals. Eur Rev Med Pharmacol Sci. 2021; 25: 2748-2751.
12. George PM, Wells AU, Jenkins RG. Personal View Pulmonary fibrosis and COVID-19 : the potential role for antifibrotic therapy. Lancet Respir. 2020; 8: 807-815.
13. Coronavirus-2019/advice-for-public, available from-https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public [Accessed on 2nd May 2021].
14. Vasarmidi E, Tsitoura E, Spandidos DA, Tzanakis N, Antoniou KM. Pulmonary fibrosis in the aftermath of the COVID-19 era. Exp Therap Med. 2020; 20: 2557-2560.
15. Grillo F, Barisione E, Ball L, Mastracci L, Fiocca R. Lung fibrosis: an undervalued finding in COVID-19 pathological series. Lancet Infect Dis. 2021; 21: e72.
16. Gentile F, Aimo A, Forfori F, Clemente A, Cademartiri F. COVID-19 and risk of pulmonary fibrosis: the importance of planning ahead. 2020. Eur J Preventive Cardiol. 2020; 27: 1442-1446.
17. Udwadia ZF, Koul PA, Richeldi L. Post-COVID lung fibrosis: The tsunami that will follow the earthquake. Lung India. 2021; 38: 41-47.
18. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: a systemic review and meta-analysis. Sci Rep. 2021; 11: 16144.
19. Chaudhary S, Natt B, Bime C, Knox KS, Glassberg MK. Antifibrotics in COVID-19 Lung Disease: Let Us Stay Focused. Front Med. 2020; 7: 539.
20. Garcia-Revilla J, Deierborg T, Venero JL, Boza-Serrano A, Garcia-Revilla J, Boza-Serrano A. Hyperinflammation and Fibrosis in Severe COVID-19 Patients: Galectin-3, a Target Molecule to Consider. Front Immunol. 2020; 11: 1-6.

21. Antoniou K, Markopoulou K, Tzouvelekis A, Trachalaki A, Vasarmidi E, Organtzis J, et al. Efficacy and safety of nintedanib in a Greek multicentre idiopathic pulmonary fibrosis registry: A retrospective, observational, cohort study. ERJ Open Res. 2020; 6: 00172-2019.
22. Margaritopoulos GA, Trachalaki A, Wells AU, Vasarmidi E, Bibaki E, Papastratigakis G, et al. Pirfenidone improves survival in IPF: Results from a real-life study. BMC Pulm Med. 2018; 18: 177.
23. Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome composition China., and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe. 2020; 27: 325-328.
24. Chan JF, Kok KH, Zhu Z, Chu H, To KK, Yuan S, et al. Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. Emerg Microbes Infect. 2020; 9: 221-236.
25. Paules CI, Marston HD, Fauci AS. Coronavirus infections - more than just the common cold. JAMA. 2020; 323(8): 707-708.
26. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020; 579: 270-273.
27. Hui DS, I Azhar E, Madani TA, Ntoumi F, Kock R, Dar O, et al. The continuing 2019-nCoV epidemic threat of novel coronaviruses to global health - the latest 2019 novel coronavirus outbreak in Wuhan, China. Int J Infect Dis. 2020; 91: 264-266.
28. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet. 2020; 395: 507–513.
29. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science. 2020; 367: 1260–1263.
30. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. Eur Respir J. 2020; 55: 9-11.
31. Kordzadeh-Kermani E, Khalili H, Karimzadeh I. Pathogenesis, clinical manifestations and complications of coronavirus disease 2019 (COVID-19). Fut Microbiol. 2020; 15: 1287-1305.
32. Times of India article on COVID19. linkk-https://timesofindia.indiatimes.com/life-style/health-fitness/health-news/new-coronavirus-impact-on-kids-new-covid-strain-and-its-impact-on-children-all-your-questions-answered/photostory/82043986.cms?picid=82044356 [Accessed, April 2021].
33. Baas T, Taubenberger JK, Chong PY, Chui PKM. SARS-CoV virus-host interactions and comparative etiologies of acute respiratory distress syndrome as determined by transcriptional and cytokine profiling of formalin-fixed paraffin-embedded tissues. Interf Cytokine Res. 2006; 26: 399-317.
34. Wen Y, Deng BC, Zhou Y, Wang Y, Cui W, Wang W, et al. Immunological features in patients with pneumonitis due to influenza A H1N1 infection. J Investig Allergol Clin Immunol. 2011; 21: 44-50.
35. Xu J, Xu X, Jiang L, Dua K, Hansbro PM, Liu G. SARS-CoV-2 induces transcriptional signatures in human lung epithelial cells that promote lung fibrosis. Resp Res. 2020; 21: 1-12.
36. Chuang H, Ho L, Harn H. Recent Findings on Cell-Based Therapies for COVID19-Related Pulmonary Fibrosis. Cell Transplant. 2021; 30: 1-4.
37. Albert RK, Smith B, Perlman CE SD. Is progression of pulmonary fibrosis due to ventilation-induced lung injury? Crit Care Med Am Thorac Soc. 2019; 200: 140-151.
38. Mach WJ, Thimmesch AR, Pierce JT, Pierce JD. Consequences of hyperoxia and the toxicity of oxygen in the lung. Nurs Res Pract. 2011; 2011: 260482.
39. McDonald LT. Healing after Covid-19: Are Survivors at Risk for Development of Pulmonary Fibrosis? Am J Physiol Cell Mol Physiol. 2020; 320: L257-265.

40. Hadda V, Guleria R. Antifibrotic drugs for idiopathic pulmonary fibrosis: What we should know? Indian J Med Res. 2020; 152: 177-180.
41. Dimitroulis IA. Nintedanib: A novel therapeutic approach for idiopathic pulmonary fibrosis. Respir Care. 2014; 59: 1450-1455.
42. Hu Q, Noor M, Wong YF, Hylands PJ, Simmonds MS, Xu Q, et al. In vitro anti-fibrotic activities of herbal compounds and herbs. Nephrol Dial Transplant. 2009; 24: 3033-3041.
43. Agrawal PK, Agrawal C, Blunden G. Quercetin: Antiviral Significance and Possible COVID-19 Integrative Considerations. Nat Prod Commun. 2020; 15: p.1934578X20976293.
44. Huang F, Li Y, Leung ELH, Liu X, Liu K, Wang Q, et al. A review of therapeutic agents and Chinese herbal medicines against SARSCOV-2 (COVID-19). Pharmacol Res. 2020; 158: 104929.
45. Su H, Yao S, Zhao W, Li M, Liu J, Shang W, et al. Discovery of baicalin and baicalein as novel, natural product inhibitors of SARS-CoV-2 3CL protease in vitro. Biorxiv preprint. 2020.
46. Hu S, Wang J, Zhang Y, Bai H, Wang C, Wang N HL. Three salvianolic acids inhibit 2019-nCoV spike pseudovirus viropexis by binding to both its RBD and receptor ACE2. J Med Virol. 2021; 93: 3143-3151.
47. Moghaddam E, Teoh BT, Sam SS, Lani R, Hassandarvish P, Chik Z, et al. Baicalin, a metabolite of baicalein with antiviral activity against dengue virus. Sci Rep. 2014; 4: 5452.
48. Vitug LC, Santiaguel J. Nintedanib as an adjunct treatment in improving lung function of post COVID-19 pulmonary fibrosis in an elderly patient: a case report. Chest. 2021; 160: A2166.
49. Colchicine and Post-COVID-19 Pulmonary Fibrosis. Available from: https://clinicaltrials.gov/ct2/show/NCT04818489?cond=Post-COVID-19+PULMONARY+FIBROSIS+AND+%22COVID-19%22&draw=2&rank=1
50. Mahmud SH, Al-Mustanjid M, Akter F, Rahman MS, Ahmed K, Rahman MH, et al. Bioinformatics and system biology approach to identify the influences of SARS-CoV-2 infections to idiopathic pulmonary fibrosis and chronic obstructive pulmonary disease patients. Brief Bioinform. 2021; 22: 1-20.
51. Omote N, Kanemitsu Y, Inoue T, Yonezawa T, Ichihashi T, Shindo Y, et al. Successful Treatment with High-dose Steroids for Acute Exacerbation of Idiopathic Pulmonary Fibrosis Triggered by COVID-19: A Case Report. Intern Med Adv Publication. 2021; 10: 2169.
52. McGroder CF, Zhang D, Choudhury MA, Salvatore MM, D'Souza BM, Hoffman EA, et al. Pulmonary fibrosis 4 months after COVID-19 is associated with severity of illness and blood leucocyte telomere length. Thorax. 2021; 76: 1242.