



# The Role of Pulmonary Surfactant in COVID-19 Understanding

Zaineb O. Ettarhouni<sup>1\*</sup> and Aysha B. Mezoughi<sup>1</sup>

<sup>1</sup>Chemistry Department, Faculty of Science, University of Tripoli, Tripoli / Libya.

## Authors' contributions

This work was carried out in collaboration between both authors. Both authors read and approved the final manuscript.

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## ABSTRACT

**Background:** In Covid-19 the virus infects the respiratory tract in human. When lung tissue becomes diseased, the walls and lining of the alveoli and capillaries are damaged. At this point lung compliance and ventilation decrease. Pulmonary surfactant that is produced and dispersed into alveolar space, has a significant role in understanding how heavily covid-19 interferes and infects lung cells. The importance of pulmonary surfactant in alveoli is to lower surface tension at air/liquid interface in the lung. This is achieved by reducing the work of breathing and preventing alveolar collapse. The main constituent of pulmonary surfactant is dipalmitoylphosphatidylcholine (DPPC) (C<sub>40</sub>H<sub>80</sub>NO<sub>8</sub>P). It is a phospholipid containing two non polar palmitic acid C<sub>16</sub> chains as hydrophobic tails linked to a polar head group of a phosphatidylcholine (also known as lecithin).

**Rationale of the Review and Objective Method:** When DPPC molecules are in contact with a polar solvent, micelles which grow further into bilayers are formed considering their cylindrical structures. This trait makes the whole structure of pulmonary surfactant as amphipathic and surface active molecules. The head group of phosphatidylcholine in the pulmonary surfactant is attracted by polar liquid molecules causing a reduction of the liquid surface tension.

**Conclusion:** This review complements the quoted information analysing them theoretically and integrates recent advances in pulmonary surfactant research with the global pandemic.

\*Corresponding author: E-mail: z.eltarhouni@uot.edu.ly;

**Keywords:** Acute respiratory distress syndrome; air/liquid interface; alveolar compliance; COVID-19; surfactant replacement therapy.

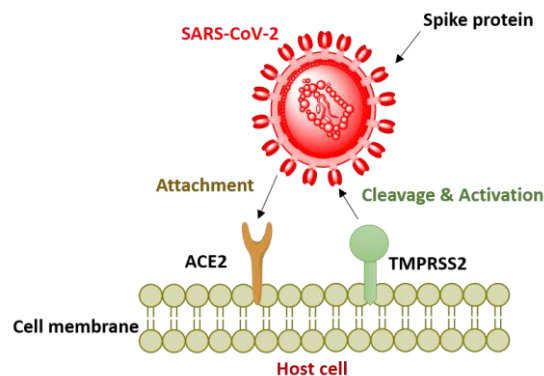
## 1. INTRODUCTION

Coronavirus diseases (COVID-19) have emerged in the late of 2019 and frequently spread and infected a large number of people around the world within a short time. The most common associated symptom is acute respiratory distress syndrome (ARDS) accompanied by hypoxemic respiratory failure and macrophage activation syndrome (MAS) [1,2]. Pulmonary embolism has been reported as severe pneumonia in some ill COVID-19 patients [3,4]. Cellular entry of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) to host human cells depends on the interactions of viral spike glycoprotein (S-protein) with extracellular receptor Angiotensin-Converting Enzyme 2 (ACE2) [5–8] similar to SARS coronavirus (Fig. 1) [9,10]. However, the affinity of SARS-CoV-2 to bind this enzyme is greater than that of SARS-CoV [11]. The receptor ACE2 attached to the lung cells membranes is expressed by type II alveolar cells (AT2) and considered to be the main target of SARS-CoV-2 [12–14]. The high expression of ACE2 in type II alveolar cells in the lung leads to virus rapidly spread causing cytokine storm syndrome hyperinflammation [15]. Consequently, inhibition of this receptor has been proposed by WHO (World Health Organization) as a critical target to discover and develop drugs for COVID-19 treatment [16]. Transmembrane serine protease 2 (TMPRSS2) and lysosomal cathepsin are responsible for Spike protein activation by cleaving it at the cell surface [17–19]. The expression of TMPRSS2 in lung tissue can raise the spread of SARS-CoV and MERS-CoV. Therefore, inhibition of this

enzyme leads to a reduction of respiratory infection caused by these viruses [17,20].

The respiratory insufficiency resulted from the loss of type II cells is basically due to the loss of pulmonary surfactant, alveolar flooding, and possible loss of normal repair. Since type II cells are the progenitors of type I cells, losing them both also blocks normal active resorption of alveolar fluid. In addition, endothelial damage is occurred and characterised by a transudation of plasma proteins, formation of hyaline membranes, and inflammatory exudate, traits of ARDS [21,22]. Ultimately, as pulmonary surfactant is essential for lung biophysical function, its deficiency or inactivity leads to lung injury and progressive failure, which is considered as the most prevalent cause of COVID-19 death rate [23–26].

The risk for contracting COVID-19 has increased in the case of elderly people with pre-existing conditions including cardiovascular disease, chronic respiratory disease, hypertension, cancer and diabetes [27]. Those patients are at risk of severe illness or death due to immune dysregulation which is represented in the impairment of the immune system and inflammatory response. The responsibility for the progression of COVID-19 infection in such cases is also related to the use of immunosuppressant and targeted immunomodulatory therapies. This group of patients should be carefully monitored and promoted to adopt the very restrictive measure in order to minimize potential exposure of COVID-19 [28].



**Fig. 1. SARS-CoV-2 entry to the host cell; This figure was adapted from the following website: (<http://www.cogershop.com/sars-cov-2-covid-19.htm?page=1>)**

In COVID-19 related ARDs, two different phenotypes have been identified including, type L (low) and type H (high) patients. The transition between the two phenotypes takes place either when the viral pneumonia gets the worst stage or from ventilator-induced lung injury. In the early stage, patients with L type display nearly normal compliance, low lung weight and recruitability, and low ventilation-to-perfusion (VA/Q) ratio. Later, H type patients show low compliance, high lung weight and recruitability [29]. Since surfactant therapy is well established to improve oxygenation and lung compliance over the last decades, an urgent need of a comprehensive research may give priority to its use as an effective treatment for H type patients.

### 1.1 Pulmonary Surfactant Composition

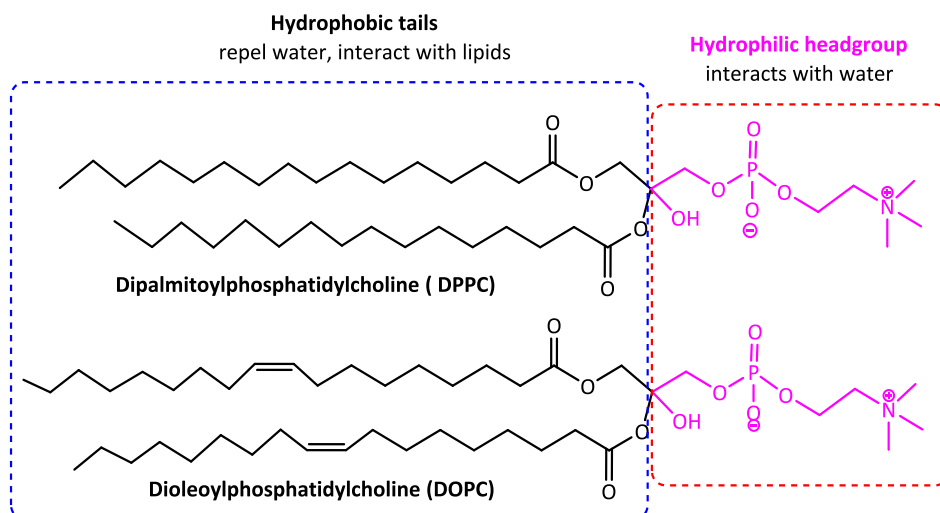
Pulmonary surfactant in mammalian lungs consists of lipids (about 85% phospholipids and 5-10 % neutral lipids) attached to proteins (SP) secreted by epithelial type II alveolar cells into the alveolar space and recycled by them in endocytosis process [30]. Phosphatidylcholine (PC) is the predominate species of the phospholipid accounts about (70-80%) of its total mass. In particular, DPPC molecules are among PC species comprising hydrophilic head groups (PC) and hydrophobic tails (palmitic acid, Fig. 2) are responsible for reducing surface tension thereby prevents alveoli collapse during the breath process [31]. Other surfactant phospholipids that exist in portions (8-15% total mass) are phosphatidylglycerol (PG) and phosphatidylinositol (PI). On the other hand, the predominate surfactant neutral lipid is cholesterol,

which is also crucial for lowering surface tension [32-35].

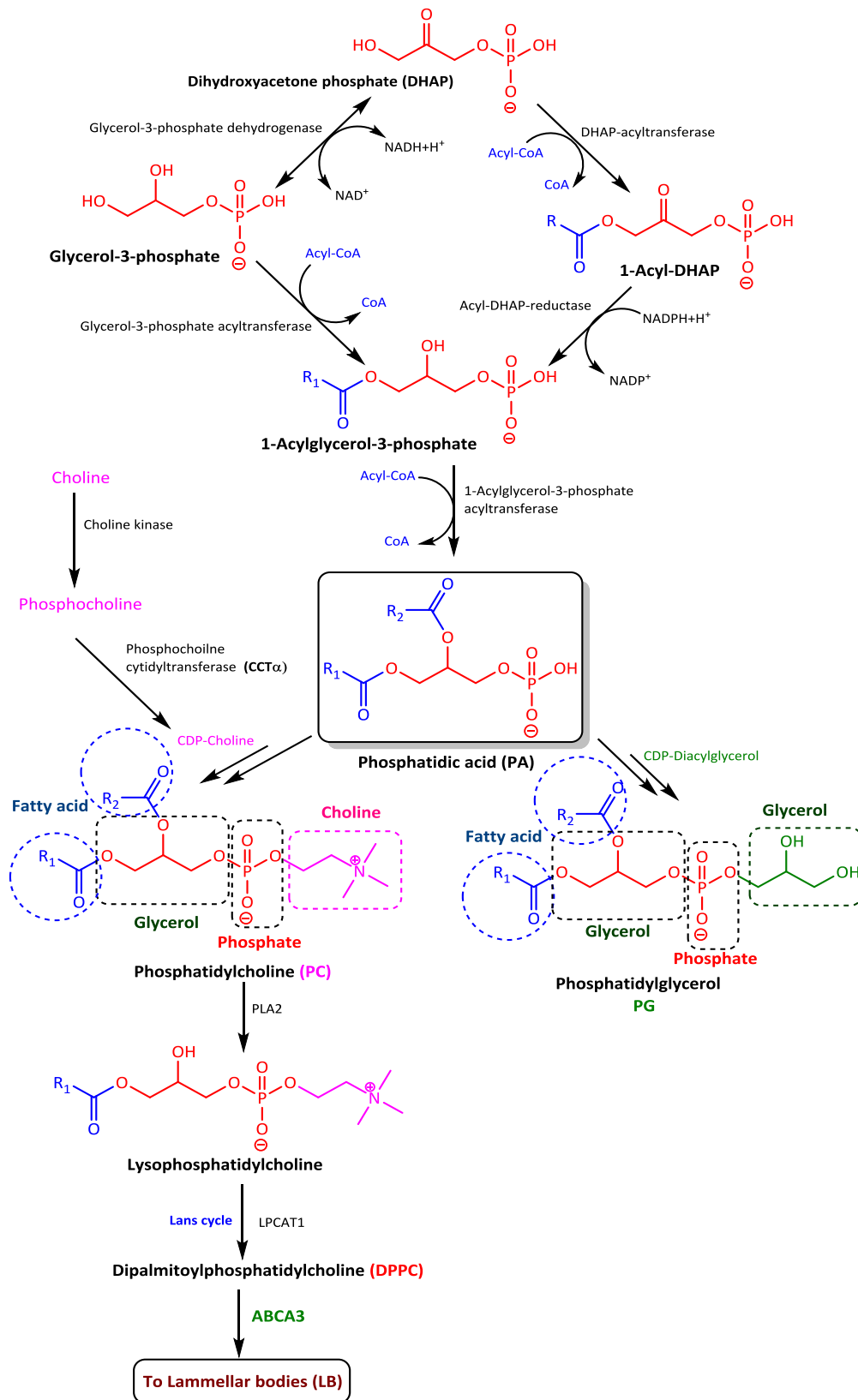
Surfactant proteins (SP) include four types: SP-A, SP-B, SP-C and SP-D. Proteins SP-A, SP-B, and SP-C are apolipoproteins attached to surfactant phospholipid, whereas SP-D is found free in lavage and could associate with phospholipid under certain conditions [35]. SP-A and SP-D are large hydrophilic glycoproteins ( collagen-containing calcium-dependent lectins) have globular domains capable to bind ligands such as carbohydrate at pathogen surface and they represent the major proteins of total surfactant weight [36,37]. SP-B and SP-C are small hydrophobic proteins that possess secondary structures rich with hydrophobic amino acids and are mostly  $\alpha$ -helix [35]. However, their amounts in total surfactant mass are very small comparing with hydrophilic surfactant proteins.

### 1.2 Synthesis and Secretion of Pulmonary Surfactant

Lung surfactant is synthesised in alveolar type II cells, particularly in its endoplasmic reticulum (ER) and passed through Golgi apparatus to store into lamellar bodies (LB) followed by its secretion into alveolar lining fluid. The synthesis of pulmonary surfactant starts by the production of precursor lipid, phosphatidic acid (PA) from dihydroxyacetone-phosphate or glycerol-3-phosphate *via* a series of enzymatic reactions as shown in Scheme 1. The synthesised phosphatidic acid is considered as the intermediate to synthesise phosphatidylcholine (PC) and phosphatidylglycerol (PG) [38-40].



**Fig. 2. Chemical structure of lung surfactant phospholipids DPPC and DOPC**



**Scheme 1. Biosynthesis of pulmonary surfactant phospholipids: phosphatidylcholine (PC), phosphatidylglycerol (PG), and dipalmitoylphosphatidylcholine (DPPC) [38–40]**

The most abundant and significant phospholipid in pulmonary surfactant, PC is synthesised via Kennedy pathway, which includes phosphorylation of choline by choline kinase followed by conversion of the product into cytidine diphosphocholine (CDP-choline). The final step of this pathway is the reaction between PA and CDP-choline to produce PC, which then remodulated by a series of enzymatic reactions affording the intracellular surfactant phospholipid DPPC. The synthesised DPPC is then translocated in the lamellar bodies (LBs) by an ATP-binding cassette transporter (ABCA) [41,42].

Pulmonary surfactant proteins are also synthesised in alveolar type II cells in addition to Clara cells. The hydrophobic proteins, SP-B, which has a dimeric structure and SP-C (a very small membrane protein) are stored and secreted in the LB with the phospholipids. Hydrophobic proteins, SP-A and SP-D both are calcium-dependent carbohydrate-binding lectins possess four core domains, N-terminus domain, collagen domain, neck region and C-terminus domains. Proteins in type II cells are assembled with the synthesised phospholipids (Fig. 3) into highly packed organelles called lamellar bodies, which then formed tubular myelin (TM) and secreted to the alveolar space [43,44].

Surfactant monolayer is essentially formed in lamellar bodies after the absorption of surfactant phospholipids to the air-liquid interface followed by its compression during exhalation and then expanded during inhalation. Within the compression process, the surface tension decreases from  $\sim 23$  mN/m to  $\sim 1$  mN/m and prevents the alveolar collapse, while expansion raises it to a high value of 20-25 mN/m. Accumulation of the used surfactant material might cause lung inflammation and injury, therefore, it is recycled into AE2C or uptake by alveolar macrophages for its catabolism [45,46].

### **1.3 The Functional Roles and Deficiency of Pulmonary Surfactant**

#### **1.3.1 Relating composition of lung surfactant to its function**

The significant function of pulmonary surfactant is to increase lung compliance allowing the lung to inflate much more easily by reducing the surface tension at the air-liquid interface during respiration as well as stop serum components infiltration in the airway [47,48]. This prevents alveolar collapse upon expiration, consequently,

assists the lungs to expand and contract. Another function of lung surfactant is the regulation of alveolar macrophage activity leading to a reduction of inflammation [49].

Intrinsically, the composition of pulmonary surfactant affects the force of the surface tension at the air/liquid interface in the lung tissue. As a thin coat of fluid covers the internal surface of the alveolus, water inside the fluid has a high surface tension, which could provide the force of collapsing the alveolus. It is well known that the surface tension of water is about 70 mN/m at body temperature. However, in the lungs it is about 25 mN/m due to the accumulation of pulmonary surfactant molecules at the alveolar-air interface. During lung deflation, the interfacial film that highly enriched in DPPC is compressed to reduce the surface tension to extremely low level. It has been believed that the surface film becomes enriched in DPPC through selective excluded of the hydrophobic SP-B and SP-C proteins and the unsaturated lipids forming a multilayer reservoir in the aqueous phase attached to the interfacial film as well as incorporates newly arriving surfactant complexes, provides stability and allows fast re-extension of the material into increasing surface area during inspiration [50–54].

When DPPC is in contact with a polar solvent, the amphipathic characteristics of its structure allow to form micelles, bilayers, and vesicles considering the bulky structure of such monomers. This advantage specifies the pulmonary surfactant with surface activity and the adsorption capacity. However, DPPC is not the most favourable structure for the adsorption features in lung surfactant, as it is in a gel phase at normal human body temperature. Some other unsaturated phospholipids such as dioleoylphosphatidylcholine (DOPC) and cholesterol, increase the surfactant fluidity by converting DPPC from its gel form to the more spreadable disordered state and then adsorbing oxygen more efficiently [55]. Basically, alveoli can be described as a gas in water interface, it is wet and surrounds a central air space. The surface tension of the alveolar fluid and its propensity to reduce the surface area, represent the alveolar collapsing force. Smaller alveoli are more difficult to inflate than larger alveoli, they are also collapsed by emptying into the larger ones. As smaller alveoli progressively promote their own collapse, small lung volumes are always linked with low compliance. A significant diminution of the collapsing force of surface

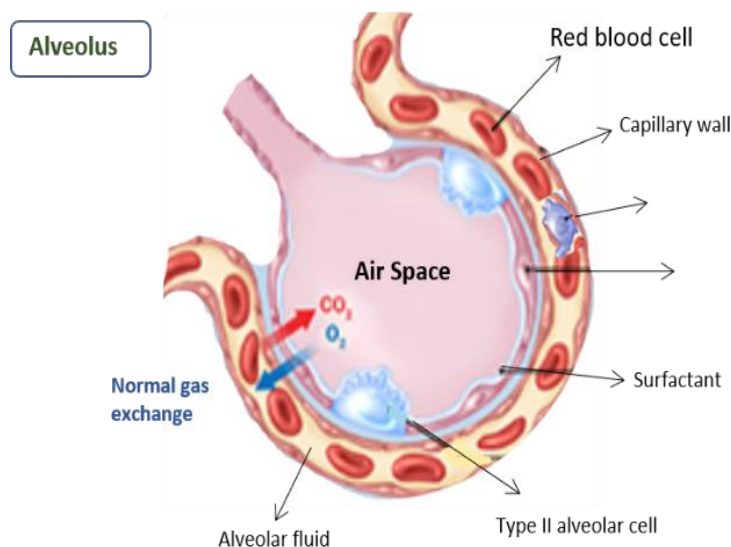
tension occurred when the hydrophilic head group of the lung surfactant is attracted by the polar molecule of the alveolar fluid in a process of generating aggregations of different structures [35].

Type I cells are extremely large, flat and critical for gas exchange (allow rapid exchange of oxygen and carbon dioxide) and trans-epithelial ion movement to keep the alveolus relatively free of fluid. These cells are also easily damaged in many forms of lung injury. For instance, the leakage of fibrinogen and other plasma proteins into the alveolus can impair the ability of surfactant to absorb to the surface and lower surface tension. Consequent to the aforementioned, higher surface tension and thus alveolar flooding in the diseased portion of the lung are strongly connected to the weakness in the composition and biophysical properties of pulmonary surfactants [56]. High alveolar surface tension would also be associated with increased transmural microcapillary pressure and microvascular leak [57].

Surfactant collectins (SP-A and SP-D) have an essential function in the lungs defence system by binding different microbes (bacteria, yeast, fungi and viruses) and protect the lungs from respiratory infections. However, they do not have a direct function in surface tension reduction [58–60]. In particular, SP-D is involved in the regulation of macrophages, neutrophils, and fibrocytes penetration. In addition, it facilitates the photogenes clearance from the lung by

alveolar macrophages and inhibits the lung inflammation, as well as plays a critical role in the surfactant normal structure and recycling by alveolar type II cells [61,62]. Moreover, serum levels of lung collectins have been reported as a biomarker for interstitial lung diseases and ARDS [63,64]. SP-D is considered as a predictive factor for the pathogenesis of severe A/H1N1 infection [65]. According to these findings and given that ARDS is a severe consequence of COVID-19 pneumonia, a study included 46 patients with COVID-19 was conducted by Kuronuma *et al.*(2020) to investigate whether lung collectins can be used as biomarkers to predict prognosis. The results of this study indicated that the concentrations of serum SP-A and SP-D significantly increased in the early stage of pneumonia. Hence and compared to the chest CT images, serum SP-A and SP-D levels are promising biomarkers for COVID-19 pneumonia prediction [66]. The advantage for using these markers is that it is easy to measure, repeatable and inexpensive [67].

The hydrophobic proteins, SP-B and SP-C are crucial to the surfactant to perform its optimal biophysical properties including the stabilisation of the alveolar and prevent its collapse as well as accelerate surfactant lipids adsorption [68–70]. In particular, SP-B is essential for surfactant lipids transfer into the air-exposed respiratory surface creating highly cohesive multilayered film at the end of expiration [30]. Consequently, it is responsible for maintaining lung air spaces open [71].



**Fig. 3. Schematic view of an alveolus and the surfactant structure (this figure was adapted from <https://www.discovermagazine.com/health/covid-19-how-does-it-affect-you>)**



### 1.3.2 Biophysical function of pulmonary surfactant

Lung surfactant or alveolar surfactant has been extensively studied for the urgent need nowadays. There has been also reported that the alveolar surface tension varied from 40 to 10 mN/m and that the tension-area characteristic exhibited a large hysteresis. Basically, during full inflation of alveoli the surfactant molecules are farther apart and the surface tension is always greater than that during deflation. This difference in the inflation and deflation curves causes surface hysteresis. However, when alveoli deflate and surfactant particles are brought closer together, alveolar surface tension decreases virtually to zero. The decrease in surface tension leads to an increase in lung compliance. The reduction of surface tension also results in a decreased capillary alveolar hydrostatic pressure and consequently decreasing ultrafiltration of fluid [72–75].

The air-water interface of alveoli is regulated by the equilibrium between the collapsing force of the surface tension and the expanding force of gas in an alveolus. The equilibrium is accomplished by the law of Laplace which describes the relationship between wall tension, pressure and radius in the alveoli [76–78].

Respiratory physiology can be described in equation 1 by the law of Laplace

$$P = 2\gamma / r \quad (1)$$

Where, P = pressure for alveolus stabilisation or the pressure difference between the inside and

the outside of the curved fluid surface, (the difference in pressure between the fluid layer and the gas inside the sphere);  $\gamma$  = surface tension at the air-liquid interface; r = radius of the spherical alveolus.

Due to the inverse relationship between the alveolus radius and pressure, the pressure required to keep alveoli open and avoid their collapse should be low at a high functional residual capacity (FRC) level.

At any given surface tension, lower compliance and higher Laplace pressure are strongly related to the smaller deflated alveoli [79]. Increasing the pressure upon the small alveoli promote their collapse since they empty into larger alveoli. Thus, fluid filtration through the pulmonary capillary wall relies on the hydrostatic pressure gradient. As this gradient adds to the alveolar surface tension, this makes fluid collect in the numerous air sacs in the lungs due to the ultrafiltration of oedema fluid in lungs [80–82]. The air flow rate is then decreased in comparison to normal, so long time is required to exhale a specific volume of air. Therefore, it causes difficulty breathing or shortness of breath. Fig. 4 illustrates the pressure difference in the alveolus based on its radius. Small alveolus deflates and large alveolus gets larger. Thus, the bigger the radius, the lower the collapsing pressure the more capable of keeping the alveoli open. Higher collapsing pressures are associated with small alveoli; they do not easily remain conspicuous [77].

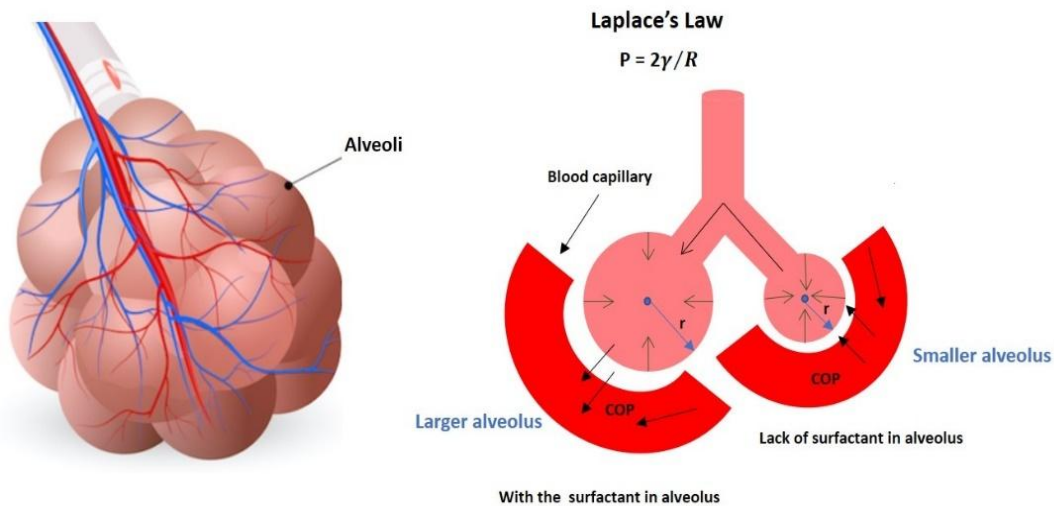


Fig. 4. A comparison between alveolus with and without the surfactant (this figure was adapted from ref. 77)

Fig. 4 shows how the absence of surfactant draws the alveolar walls inward causing a greater negative interstitial space and overcomes the colloid osmotic pressure (COP) of blood. It is also obvious from the figure that with the surfactant, a less negative interstitial space is produced due to enlarging the alveolus, thereby keeping the alveoli dry [83].

#### 1.4 Surfactant Deficiency

Pulmonary surfactant absence or deficiency produces severe lung pathologies. Shortage of surfactant components leads to neonatal respiratory distress syndrome (NRDS), which occurs in premature babies due to the late development of their lungs [84]. In this case, they need to be provided by an exogenous surfactant to begin their breathing properly until their endogenous surfactant system is matured [85]. Dysfunction of pulmonary surfactant causes acute lung injury (ALI) and severe form ARDS. In the case of ARDS, where the surface tension at air-liquid interface is high and constant due to the consumption of surfactant, the lungs can be opened with pressure half of that is needed for lung opening (20 cm H<sub>2</sub>O) [86,77]. One way of reducing the function of the lung surfactant is by the effect of oxidising agents such as free radicals, that liberated from leukocytes or other pollutants leading to various lung diseases [87,88]. Disturbing surfactant homeostasis by smoking or pollution as examples, leads to surfactant insufficiency or accumulation. In a similar way, surfactant homeostasis is affected throughout acute respiratory distress syndrome (ARDS) [54].

Deficiency of collectins production increases the sensitivity to respiratory infections and lung inflammation [89]. According to a reported study in 2007 by Leth-Larsen et al., which revealed the probability of preventing the inflammation of pulmonary surfactant due to the possible interaction between SP-D and the carbohydrate moieties on the spike protein of SARS-CoV, Ralf Weiskirchen 2020 suggested that SP-D could interact independently as a COVID-19-related factor, thereby the shortage of this protein will influence the host innate immunity during SARS-CoV 2 infection.[90,91] The genetic deficiency of SP-B increase the fatal RDS during birth, whereas SP-C genetic deficiency causes interstitial lung disease, which connected to the loss of AE2C cells [92,93].

#### 1.4.1 Relation to the way that SARS-COV-2 virus works

Since lung surfactant preserves the alveolar stability, it presents in small airways and is stored as lamellar structures in the alveolar fluid. The host defence properties are linked to SP-A and SP-D, while SP-B and SP-C interact with surfactant phospholipids due to their hydrophobicity optimizing the function of lowering surface tension [94]. However, SP-C incorporated into liposomes of DPPC and POPG reduced the bacterial growth by inhibiting the LPS released from Gram negative bacteria. On the other hand, the deficiency of SP-C in the animal models are susceptible to viral infections.[89] SARS-CoV2 interacts with lung surfactant molecules in a very specific way (particularly DPPC accompanied by four protein based-surfactant) causing destruction of the type II cells and reduce surfactant production. Since the infection has spread from the upper parts of the respiratory tract to the deepest levels in the alveoli, the symptoms develop from asymptomatic and moderate symptoms to serious respiratory manifestations. After SARS-CoV-2 entered the lung, it starts to replicate in the alveolar type II cells and uses a single-strand RNA replication system of these cells to produce many copies of the virus's RNA and spread to other cells in the body. Consequently, it causes tremendous harm and influences the production and turnover of pulmonary surfactant accompanied by alveolar collapse and inflammation as well as flooding, which leads to alarmingly poor blood oxygenation. Therefore, pulmonary surfactant is required for an effective gas exchange due to the passage of blood through the pulmonary capillaries. As the entry of SARS-CoV 2 to the host cells is through ACE2 enzyme in the membrane of alveolar type II cells, these cells are then destroyed by the viral infection [95–97].

The lipid membrane in the structure of SARS-CoV 2 represents the hydrophobic domain comprises its vital proteins and RNA. Viral occupation and proliferation altered surfactant production followed by dyspnea and acute respiratory distress syndrome (ARDS) leading to lung failure and death in serious COVID-19 patients [98, 99]. The infection mechanism relies on the ability of the virus to maintain its integrity and pass the alveolar cells. This process is driven by the integrity of the lipid membrane, along with embedded spike proteins [100].



The virus survival time on a surface was reported to be on the order of hours [101]. The respiratory droplets which are produced during sneezing, coughing, and moist speaking are likely to be a source of secondary infection on the surfaces. It is highly required to understand these infected droplets on the surfaces and their duration in order to identify the mechanism of the virus transmission. Therefore, it is crucial to consider the factors affecting the drying time such as surface contact angle, type of the surface, droplet size, pH, temperature and other ambient conditions. Studying the long survival time of the virus on surfaces requires considering the volume of the respiratory droplets, the way that they evaporate the initial virus concentration [102,103]. Characterizing such important elements influences the way that COVID-19 works.

#### 1.4.2 Treatment of COVID-19 with reducing surface tension

There will be an increasing significance of studying biosurfactants in dealing with the pandemic. They possess remarkable low cytotoxicity in addition to natural and sustainable characteristics. Surfactant replacement therapy has been established as an appropriate preventive and treatment for surfactant deficiency-related diseases such as respiratory distress syndrome (RDS). The major benefit from this treatment is alveolar surface tension reduction in premature infants who are born before the biosynthesis of surfactant is completed (before 35 weeks of gestation) and they suffered from RDS [104]. Exogenous lung surfactant can improve gas-exchange in lungs and decreases mortality by RDS [105]. Generally, the desired results of the surfactant therapeutic depend on the place of viral infection (i.e. conducting airway, alveoli, nose) [90].

Commercially available surfactants that are used for these purposes can be either natural

surfactants (extracted from animal lungs) or synthetic surfactants. Surfactants from natural source enhanced infant survival much better than the synthetic one [106]. The most common surfactants that are used in surfactant therapy are listed in Table 1 [107]. The surfactant reaches all parts of the infant's lungs through different methods for surfactant delivery, which can be prophylactic (immediately after birth) or secure (after the diagnosis of RDS) [108]. These delivery techniques include endotracheal tube approach (ETT) followed by mechanical ventilation or without intubation such as aerosolization, pharyngeal instillation, laryngeal mask administration and tracheal catheterisation [109].

Studying the feasibility and safety of surfactant and its impact on mortality are the key elements to establish its true efficacy in treatment. In COVID-19 patients, surfactant delivery strategies including bronchoscopic form are proven to reduce or prevent endotracheal intubation and the duration of mechanical ventilation (MV). As liquid surfactant delivery is practical and well tolerated, acute decompensation could be avoided by the meticulous bronchoscopic delivery [29].

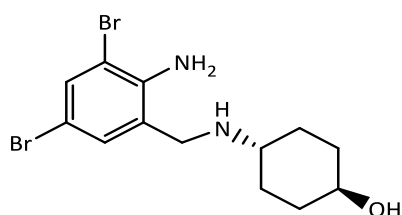
Drug administration issues could affect the advantage of using surfactants as a therapy. This includes the aspects of clinical trial design such as timing of surfactant dosing and the administration method. The insufficient drug in the dosing procedure could also stop the surfactant from reaching the alveoli in the adult lung as the required uniform distribution over the surface area of the airways is hard to be achieved [110]. Undoubtedly, if these drug administration issues are dissipated, a logical argument exists for using surfactant treatment procedure for H type COVID-19 patients.

**Table 1. Potential surfactants approved for clinical use**

S. Class	S. Name	S. Source	S. Origin	S. Regist. trademark	S. Clinical dose mg/kg
Natural	Poractana alfa	Minced tissue	Porcine	Curosurf®	100/200
	Beractant	Minced tissue	Bovine	Survanta®	100
	Bovactant	BAL	-	Alveofact®	50
	Calfactant	-	-	Infasurf®	100
	Lusupultide	-	-	Venticute®	50
	Colfosceril	-	-	Exosurf®	67
Synthetic	Lucinactant	-	-	Surfaxin®	175
	CHF5633	-	-	-	100/200

It has been suggested that treatment of patients with COVID-19 pneumonia in the early stage by natural lung surfactant could decrease the ventilation therapy period by raising blood oxygenation, improve the immoderate inflammatory reaction in the lung and reduce pulmonary oedema, which all lead to increasing patients recovery [75,111]. A natural surfactant, Curosurf has been safely used for COVID-19 patients treatment at a clinical dose of (720 mg/150 ml normal saline), which delivered through bronchoscopy resulted decrease of mechanical ventilation and mortality.[90] However, identifying the virus attack route may help in the development of targeted therapies. This includes either replacing the depleted lung surfactant or protecting type II alveolar cells to maintain the surfactant secreting function [112].

Among several efforts that were directed toward finding an effective treatment for COVID-19, Pradeep Kumar proposed a hypothesis about using surfactant-ambroxol co-aerosolized as a physical therapeutic intervention approach for COVID-19 related ARDS [113]. This hypothesis is based on the function of ambroxol (2-amino-3,5-dibromo-N-[trans-4-hydroxycyclohexyl]benzylamine) as a potent stimulant of surfactant production and its assistance of surfactant lipid secretion by alveolar type 2 cells as well as its activities as an anti-inflammatory and antioxidant agent [114–117]. Moreover, ambroxol alone has been used as an effective and well tolerated treatment for both acute and chronic respiratory diseases in both adults and children [118]. Taking all information together, DPPC-ambroxol intervention could prevent lung injury and reduce the capillary permeability, that caused by SARS-CoV 2 infection, if it is used at the early stage of COVID-19. It has also been suggested that developing this hypothesis by nebulizing DPPC as nanovesicles coated with ambroxol improves its binding to the lung lining.



**Fig. 5. Chemical structure of ambroxol**

In another study, Pramod and Coworkers investigated using surfactant as a preventive

treatment against COVID-19 [119]. Their hypothesis based on the entry of SARS-CoV 2 to the human body through mouth, nose and eyes. Consequently, they supposed that the virus can be deactivated by using surfactant-based gargle, surfactant-loaded throat paint, mouthwash, nasal drops, and eye drops.

## 2. CONCLUSION

People of all ages at higher risk of getting serious symptoms of the infectious disease caused by the most recently discovered coronavirus. While, people with several chronic conditions, including type 2 diabetes, severe obesity and serious heart diseases, are more likely to experience even more dangerous symptoms if infected with COVID-19. Surfactants, which suggested to be an ideal candidate to behave as a cure, are urgently recalled by many scientists. Since they are potentially proven in behaving safely and effectively as cleaning solutions, surfactants exhibit medicinal qualities for coronavirus treatment. Here, pulmonary surfactant characteristics are elucidated considering their ability of reducing virus impacts inside human lung. Interestingly, the surfactant structure plays a crucial role in its precise function. The hydrophilic head groups and the lipophilic tails and their interactions with the virus structure are widely studied over the past year. The strong relationship between the lung compliance and reducing the surface tension in the air-water interface in the alveoli was the essence of such studies. The decrease in surface tension leads to an increase in the lung compliance. Basically, the reduction of surface tension results in a decreased capillary alveolar hydrostatic pressure and consequently decreasing ultrafiltration of fluid.

In particular, the identification of the virus structure provides better understand how the hydrophobic domain of the virus is disrupted by the amphiphilic nature of biosurfactants. Additional studies are needed in order to minimize the high level of the widespread of pandemic coronavirus and its impacts, also to combat the consequences of this virus and pathogens in the future.

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## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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