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Biosurfactants and anti-inflammatory activity: A potential new approach towards COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) has grown to be global public health emergency. The biosurfactants (BSs) are surface-active biomolecules with unique properties and wide applications. Several microbes synthesize secondary metabolites with surface-active properties, which have a wide range of anti-inflammatory and anti-viral roles. The monocytes and neutrophils are activated by bacteria, which subsequently result in high secretion of pro-inflammatory cytokines (TNF- α , IL-6, IL-8, IL-12, IL-18 and IL-1 β) and toll-like receptors-2 (TLR-2). Following the inflammatory response, BSs induce the production of cationic proteins, reactive oxygen species (ROS) and lysozyme, and thus can be used for therapeutic purposes. This article provides recent advances in the anti-inflammatory and antiviral activities of BSs and discusses the potential use of these compounds against COVID-19, highlighting the need for in-vitro and in-vivo approaches to confirm this hypothesis. This suggestion is necessary because there are still no studies that have focused on the use of BSs against COVID-19.

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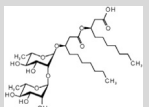
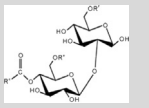
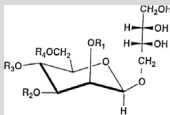
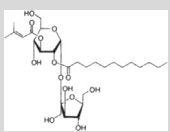
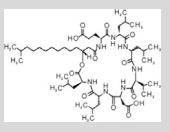
SARS-CoV-2, Biosurfactants (BSs), Immunomodulatory, Microorganisms, Cytokine storm.

Introduction

Surfactants are molecules with amphipathic properties having hydrophilic and hydrophobic moieties that reduce surface and interfacial tension between liquids or biphasic systems as liquid/gas, liquid/liquid and solid/liquid. Based on the origin, the surfactants have been classified into chemical surfactants and biosurfactants (BSs) [1]. BSs are secondary metabolites obtained from several microorganisms including bacteria, fungi and yeasts; classified based on their chemical composition and their origin from microbes, including *Pseudomonas aeruginosa*, *Bacillus subtilis* and *Lactobacillus* sp. [2]. They are attached either intracellularly or extracellularly during growth [3]. BSs are used in a wide range of applications since it is eco-friendly and biodegradable than synthetic surfactants. In recent years, this has attracted broad interest due to their unique properties like specificity, low toxicity and smooth preparation. These properties have gained attention in broad areas of cleaning and other applications for commercialization [4]. The unique features of BS opted for industrial applications such as petroleum, fertilizers, cosmetics,

Table 1

Classification of biosurfactants and its role in various potential medical applications.

Biosurfactant		Structure	Microorganism	Potential medical applications	Reference
Group	Class				
Glycolipids	Rhamnolipids		<i>Pseudomonas aeruginosa</i> , <i>Pseudomonas chlororaphis</i> , <i>Pseudomonas fluorescens</i> , <i>Pseudomonas luteola</i> , <i>Pseudomonas putida</i> , <i>Pseudomonas stutzeri</i> , <i>Burkholderia glumae</i> , <i>Burkholderia plantarii</i> , <i>Burkholderia kururiensis</i> , <i>Burkholderia pseudomallei</i> <i>Streptococcus mutans</i> , <i>Streptococcus oralis</i> , <i>Streptococcus sanguinis</i> , <i>Neisseria mucosa</i> , <i>Actinomyces naeslundii</i> .	Anti-microbial activity, cytotoxic activity	[13,53–58]
	Sophorolipids		<i>Torulopsis bombicola</i> , <i>Candida bombicola</i> , <i>Rhodotorulabogoriensis</i> , <i>Candida albicans</i> , <i>Candida glabrata</i> , <i>Rhodotorulababjevae</i> , <i>Wickerhamielladomercqiae</i>	Anti-viral, anti-microbial, anti-inflammatory and anti-fungal activity	[12,27,55,59–66]
	Mannosylerythritol lipids		<i>Pseudozyma antarctica</i> , <i>Ustilagomaydis</i>	Anti-microbial activity, anti-oxidant activity, immunological and neurological property	[35,67–69]
Lipoprotein	Trehalolipids		<i>Rhodococcus erythropolis</i> , <i>Nocardia erythropolis</i> , <i>Mycobacterium</i> sp., <i>Arthobacter</i> sp., <i>Corynebacterium</i> sp.	Anti-viral activity against herpes simplex virus and influenza virus	[69]
	Surfactins/viscosin		<i>Bacillus subtilis</i> , <i>Bacillus licheniformis</i> , <i>Pseudomonas libanensis</i> , <i>Pseudomonas fluorescens</i>	Anti-coagulant, anti-mycoplasma, anti-viral, anti-bacterial, anti-inflammatory	[56,58]

chemicals, foods, pharmaceuticals and more. They are also used as emulsifiers, demulsifiers, foaming agents, food ingredients and detergents. Generally, the BSs are used in hand washes and for personal hygiene purposes to prevent the viral transmission, get rid of viral disease symptoms, acts as drug transport and also as anti-viral facemasks [4]. An essential property of BS is the surface and interfacial tension. Surface tension is defined as the tension created between attractive intermolecular forces in a molecule. The ability to minimize the surface tension determined by the concentration of the surface-active compound called critical micelle concentration (CMC). The CMC is the minimum concentration required to reduce the surface tension and induce micelle formation. The primary function of BS is to control the attachment and detachment of microorganisms from the surfaces [5]. The structure of BS depends on the presence of hydrophobic and hydrophilic moieties. Hydrophilic moiety consists of peptides, amino acids, mono-, di- and polysaccharides, whereas hydrophobic moiety consists of saturated and unsaturated fatty acids. The BSs are differentiated based on molecular mass where the lower molecular mass molecules reduce the surface, and interfacial tension and the higher molecular weight efficiently function as emulsion balancing agents. Based on molecular mass, the BSs are classified as glycolipid, phospholipid, lipoprotein or lipopeptide, polysaccharide-lipid complex or microbial cell surface. Microorganisms also produce chemical-based surfactants known as polymeric microbial surfactants. Hence, the physiochemical properties of BSs and their biomedical applications with the source and chemical structure have been distinguished. The classification of BSs from various organisms and studies with biomedical importance has been tabulated in Table 1.

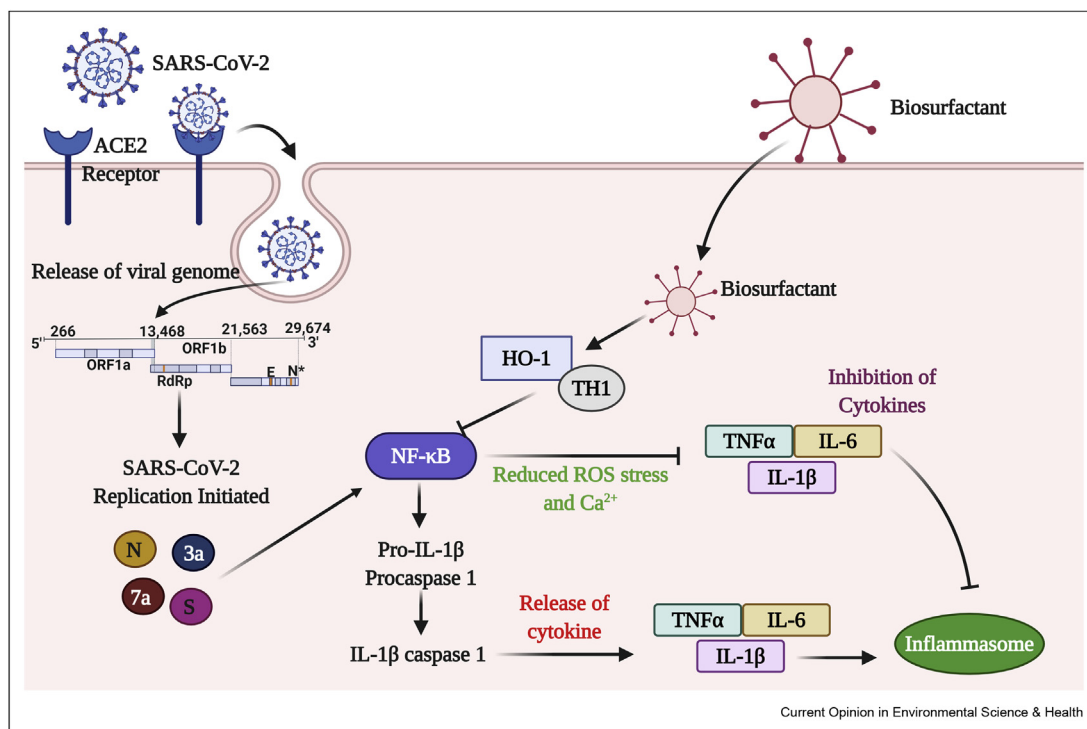
Coronavirus disease 2019 (COVID-19), caused by a new strain of coronavirus emerged in December 2019 and became a global pandemic. The COVID-19 has grown to be a global public-health emergency [6]. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a new member of the genus beta coronavirus, which exhibits faster human-to-human transmission leading to a worldwide public health emergency [7,8]. Once infected, the patient mainly relies on the immune system to resist SARS-CoV-2, with the supportive treatment being prescribed if complications occur [9]. Meanwhile, scientists confirmed that the first step in the SARS-CoV-2 pathogenesis is the specific interaction of the virus with angiotensin-converting enzyme 2 (ACE2), a master regulator of the renin-angiotensin system of host cells through its spike protein [10]. Once the virus enters the lungs, the immune system sends a large number of immune cells to kill the virus [11]. Once the cytokine storm is formed, the immune system is exaggerated and kills the healthy cells [12]. Besides, the ability of the virus to evade, the immune system is hugely problematic when considering appropriate treatment and vaccine options.

SARS-CoV-2 debilitates the equilibrium maintained by the immune system and triggers the cytokine storm. The significant difficulties found in COVID-19 patients have been linked to the cytokine storm. In-depth research is required to effectively manage the cytokine storm while maintaining the immune system balance. On binding, the spike protein is cleaved into two, and this induces a conformational change facilitating the fusion of the virus and its entry into the cell. Recently, Vellingiri et al. [6] comprehensively discussed about the viral transcription, translation and expression of viral proteins in the cells. BSs in medical application has elevated during the past decade. BS acts as a therapeutic agent due to its anti-viral, anti-bacterial and anti-fungal property in fighting many diseases [13]. Hence, this review focuses on the anti-inflammatory and anti-viral properties of the BSs, and its potential uses against as a strategy to treat or prevent COVID-19 disease.

Anti-inflammatory potential of biosurfactants

Phospholipase A₂ (PLA₂) functions in arachidonic acid (AA) secretion. Various types of PLA₂ collectively called as cytosolic phospholipase-A2 (cPLA₂). Inflammatory response occurs due to the release of AA that is converted to inflammatory mediators. AA acts as a precursor of eicosanoids secretion, which functions in maintenance of inflammatory process. Mechanistically, structural features of BSs were detected by toll like receptors (TLR-2), and the BSs communicate with the cell membranes and macromolecules and inhibit cPLA₂ that initiate anti-inflammatory responses. In an *in vitro* model, the pro-inflammatory cytokines were secreted by neutrophils when induced with trehalolipids synthesized by *Rhodococcus ruber* [14]. The glycolipids from *R. ruber* were induced in mononuclear cells, and it was revealed to mediate the production of interleukin-12 (IL-12), interleukin-18 (IL-18) and reactive oxygen species (ROS) [15] and stimulated the production of TNF- α , IL-1 β and IL-6 [16]. Administration of surfactin in rat and fish models decreased the pro-inflammatory cytokines with an increase in the levels of anti-inflammatory cytokines [17,18]. The BS surfactin from *Bacillus subtilis* was observed to suppress lipopolysaccharide-induced signaling pathways, impaired macrophage function and IL-12 expression, decreased TLR-4 protein expression with an increase in the anti-inflammatory effect [19]. Surfactin from *Staphylococcus aureus* significantly reduced the pro-inflammatory cytokines, obstructed the lipoteichoic acid-induced signaling pathway, increased STAT-3 phosphorylation and blocked the expression of heme oxygenase-1 (HO-1). It has been established that surfactin as an anti-inflammatory and neuroprotective agent [20]. Similarly, limited studies were conducted, and they revealed the potential effect of BSs from yeast species with anti-inflammatory activity. Sophorolipids (SLs) from *Candida bombicola* decreased immunoglobulin

Figure 1



Anti-inflammatory role of biosurfactants (BSs) against COVID-19: The above image depicts the hypothetical role of BSs as anti-inflammatory agents against COVID-19. When the SARS-CoV-2 enters the cell, it binds to the ACE2 receptor following which the TMPRSS2 helps in the cleavage of S protein into S1 and S2 subunits. Subsequently, the viral replication gets initiated resulting into NF-κB pathway, which stimulates the release of cytokine storm. In this condition, providing the COVID-19 patients with BSs along with other drugs promises to suppress the production of NF-κB by triggering the heme-oxidase 1 and TH1 macrophages, which in turn would reduce the effect of cytokine storm and inflammation in the patients affected with COVID-19.

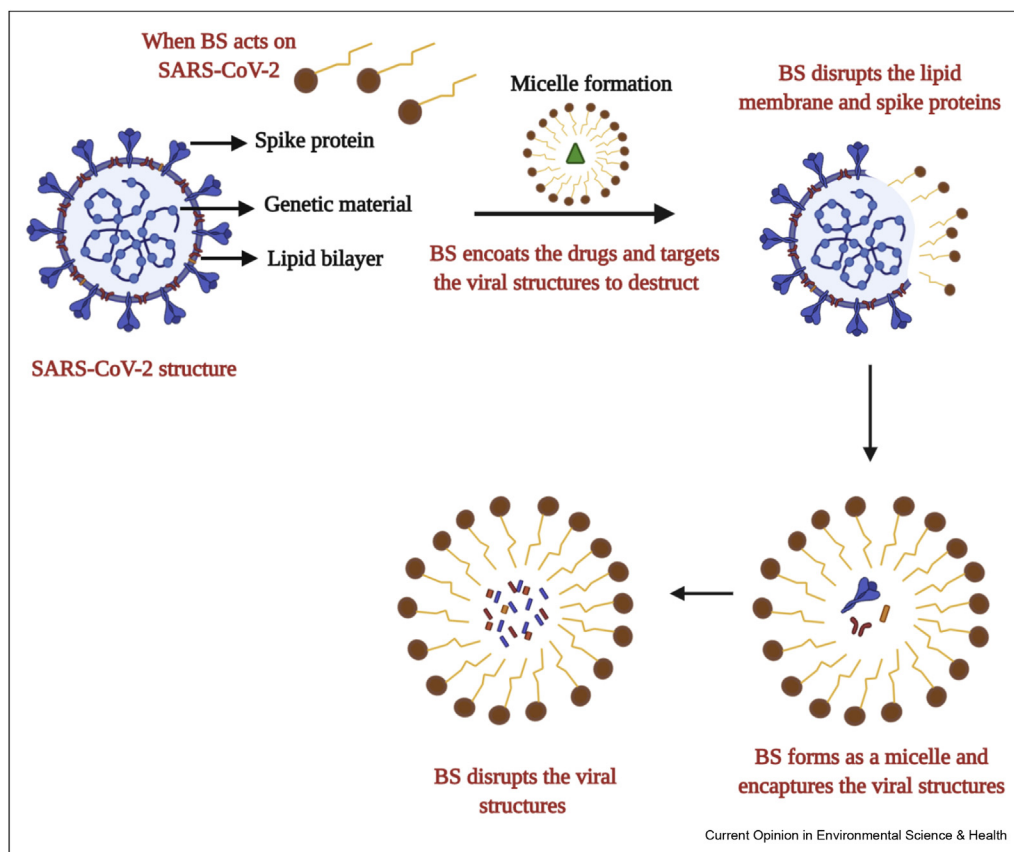
E (IgE) level, mRNA expression of TLR-2, IL-6 and STAT3 and lung inflammation [21,22]. Hence, the study demonstrated that SLs downregulate the IgE coding genes, thereby acting as an anti-inflammatory agent and potential therapeutic compound [21,23]. In an experimental rat model, SLs reduced sepsis-related mortality and observed predicted to display anti-inflammatory effects [24,25]. Similarly, in another rat model study, SLs resulted in an improved survival rate, decreased nitric oxide and modulated inflammatory responses [26]. Natural and synthetic SLs were demonstrated to show a prominent anti-inflammatory activity, spermicidal and anti-HIV activity [27]. The SLs reduce the expression of inflammatory cytokines [25] and these findings indicate that SLs would be a promising therapy for anti-inflammatory or immunomodulation in chronic inflammatory conditions. Mannosylerythritol lipids are secreted by *Pseudomonas antarctica*, which has also inhibited the inflammatory mediators, thereby creating anti-inflammatory action [28]. From these studies, it is clarified that the BSs from bacterial and yeast species showed an anti-inflammatory activity and suggested to be potential therapeutic candidate in treating inflammatory diseases. Also, more studies need to be

conducted on the effects of anti-inflammation using these BSs.

Biosurfactants anti-inflammatory role against COVID-19

Once the SARS-CoV-2 enters the human host cell through the ACE2 receptors, immediately the immune system deploys a large number of immune cells to respond against the virus especially by recruiting the antigen-presenting cells [29]. It is reported that the COVID-19-positive patients have high levels of cytokine storm, which are also correlated with the viral load in COVID-19 patients [30]. When the cytokine storm is formed, the immune system is exaggerated and kills healthy cells [12]. Moreover, when the levels of IL-6 and lymphocytes are higher, they inadvertently result in increased pulmonary damage [31]. In addition to this, the ability of the virus to evade the immune system is hugely problematic when considering appropriate treatment and vaccine options. The subsequent damage can be caused either by direct infection of SARS-CoV-2 in cells, by hypoxemia due to lung damage or by an indirect injury caused by the immune and cytokine responses [32]. Excessive amounts of cytokines, such as

Figure 2



Possible anti-viral activity of biosurfactants (BSs) on SARS-CoV-2: On SARS-CoV-2 infection, BSs act on viral structures (spike protein and lipid envelope) and ruptures the outer membrane and makes the virus inactive by targeting the genetic material. Once the viral structures are disrupted it forms as a micelle and engulfs the structural parts and breaks down the materials to make it inactive.

IL-1 β and IL-18, are produced during the cytokine storm and may cause irrevocable damage to various organs. It is well known that the BSs have a major role in defense against pathogenic infection as well as induce anti-inflammation in the human body [33]. The glycolipid and lipopeptide types of BSs have been effectively used towards treating various anti-microbial diseases [34]. One of its types, the surfactin, which is a natural cyclic lipopeptide, has shown to have various biological properties like anti-viral, anti-fungal and anti-cancer, which is initiated by suppressing the signaling of cell survivals, platelet aggregation and reducing the cytokine storm by proposing anti-inflammatory effects [35]. Hence, the use of BS would be a possible way to minimize the impact of cytokine storm caused due to SARS-CoV-2 infection in the COVID-19-affected patients. We propose a hypothetical mechanism of action of BS in reducing the inflammation in the COVID-19 disease. On binding of the SARS-CoV-2's the S (Spike) protein, it is cleaved into two; this induces a conformational change facilitating the fusion of the virus and its entry into the cell. The NF- κ B pathway is a common pathway

implicated in many pathologies and is activated by viral N, S, 3a and 7a proteins. NF- κ B, on activation, enters the nucleus and catalyses the transcription of pro-IL-1 β and procaspase-1. When additional signals like increased Ca²⁺ and ROS are detected, the pro-IL-1 β and procaspase 1 are cleaved into IL-1 β and caspase 1. This results in the production of cytokines such as (TNF- α , IL-1B, IL-6, IL-2) and causes a cytokine storm that results in necrosis and cell death. In COVID-19 patients, it is observed that there is an inhibition in the production of heme, as it is responsible for the production of biliverdin, ferrous iron and carbon monoxide, which could limit the inflammation and stress caused due to SARS-CoV-2 viral infection [36–38]. If the BS is provided to the COVID-19 patients, then it could suppress the production of NF- κ B by stimulating the HO-1 and TH1 macrophage cells [39]. This, in turn, would reduce the production of cytokines such as TNF- α , IL-1B, IL-6, IL-2, which will reduce the effect of cytokine storm in the COVID-19 patients. This possible mechanism has been depicted in Figure 1. Even it has been reported that as the BSs are known for its

Table 2

List of clinical trials using surfactant compounds as a therapeutic agent against respiratory diseases.

S.No	Study	Intervention	Disease	Study size	Description	Status	Country
1.	Surfactant Administration Via Thin Catheter Using a Specially Adapted Video Laryngoscope	Curosurf	RDS	20	Surfactant administration via thin catheter using a specially adapted VN scope	Active, not recruiting	Israel
2.	Surfactant for Neonate with Acute Respiratory Distress Syndrome (ARDS)	Surfactant	ARDS	200	Surfactant combined with mechanical ventilation (MV) is given to the infant with ARDS	Recruiting	China
3.	Aerosolized Surfactant in Neonatal RDS	Surfactant	RDS	159	Dose: 100 mg phospholipid/kg and 200 mg phospholipid/kg	Active, not recruiting	United States
4.	Effects of Bolus Surfactant Therapy on Peripheral Perfusion Index and Tissue Carbon Monoxide	Poractant alfa Beractant	RDS	48	Poractantalfa: 200 mg/kg for n = 15 or beractant: 100 mg/kg for n = 15 were administered in a consecutive randomized manner within the first 6 h of life	Completed	Turkey
5.	First in Human Study on Synthetic Surfactant CHF 5633 in Respiratory Distress Syndrome	Synthetic surfactants	RDS	40	CHF5633 200 mg/kg synthetic surfactant sterile suspension in 3.0 mL glass vials with a total concentration of 80 mg/mL for intratracheal administration. Single administration	Completed	United Kingdom
6.	Surfactant Via Endotracheal Tube vs. Laryngeal Mask Airway (LMA) in Preterm Neonates with Respiratory Distress Syndrome	Remifentanyl	RDS	130	Additional premedication in the endotracheal intubation/INSURE arm	Recruiting	United States
7.	A Multicenter, Randomized, Open Label Trial of a New Animal Extracted Surfactant to Treat RDS in Preterm Infants	Butantan	RDS	327	Butantan surfactant: 100 mg/kg, IT, maximum of 3 doses	Completed	Brazil
8.	The Effect of Surfactant Dose on Outcomes in Preterm Infants with RDS	Surfactant	RDS	2600	Two doses: 100–130 mg/kg and 170–200 mg/kg	Recruiting	United Kingdom
9.	Laryngeal Mask Airway (LMA) for Surfactant Administration in Neonates	Curosurf	RDS	103	–	Completed	United States
10.	Very Early Surfactant and NCPAP for Premature Infants with RDS	Surfactant	RDS	278	–	Completed	Colombia
11.	Surfactant Positive Airway Pressure and Pulse Oximetry Trial (SUPPORT) in Extremely Low Birth Weight Infants	Surfactant	RDS	1316	–	Active, not recruiting	France
12.	Exogenous Surfactant in Very Preterm Neonates Presenting with Severe Respiratory Distress in Prevention of Bronchopulmonary Dysplasia	Curosurf	RDS	100	2.5 mL/kg instilled in the trachea	Active, not recruiting	France
13.	Surfactant Application During Spontaneous Breathing with CPAP or During Mechanical Ventilation in the Therapy of IRDS in Premature Infants <27 Weeks	Curosurf	RDS	213	Conventional therapy with intubation, initiation of MV and surfactant application	Completed	Germany
14.	Exosurf Neonatal and Surfactant for Treatment of Respiratory Distress Syndrome	Exosurf	RDS	617	Infants received up to four intratracheal doses of the surfactant	Completed	United States
15.	Pilot Trial of Surfactant Booster Prophylaxis for Ventilated Preterm Neonates Less than or Equal to 1250 gm Birthweight Ver 4.0	Infasurf	RDS	89	Infasurf 3 cc/kg instilled via endotracheal tube, repeated 3 and 7 days later if infant stable and continues to meet criteria	Completed	Philadelphia
16.	Perfusion Index Variability in Preterm Infants Treated with Two Different Natural Surfactants for Respiratory Distress Syndrome	Beractant Poractant alfa	RDS	92	Beractant; both initial and subsequent dosing are 100 mg/kg (4 mL/kg), which may be given every 6 h up to four total doses. Porcine lung extract, initial dosing is 200 mg/kg (2.5 mL/kg), and repeated	Completed	Turkey

(continued on next page)

Table 2. (continued)

S.No	Study	Intervention	Disease	Study size	Description	Status	Country
17.	Pilot Trial of Surfactant Therapy For Preterm Neonates 5–21 Days Old With Respiratory Decompensation	Infasurf	RDS	11	dosing is given at 100 mg/kg (1.25 mL/kg) every 12 h, up to maximum of two additional doses when indicated Infasurf 3 cc/kg instilled via endotracheal tube q 12–24 h x 2 doses	Completed	Philadelphia
18.	Comparison of Curosurf and Infasurf in the Treatment of Preterm Infants with Respiratory Distress Syndrome	Calfactant Poractant alfa	RDS	30	–	Completed	Columbia
19.	Curosurf in Adult Acute Respiratory Distress Syndrome Due to COVID-19	Poractant alfa	COVID-19 ARDS	20	–	Recruiting	France
20.	Curosurf/Budesonide for Infants with Respiratory Distress Syndrome	Budesonide	RDS	300	–	Completed	China
21.	Comparison of Four Influenza Vaccines in Seniors	Agriflu Fluad Intanza Vaxigrip	Influenza	953	Each with 0.5 mL dose IM vaccination	Completed	Canada

RDS, respiratory distress syndrome; ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019.

emulsification role in drugs or vaccines would be highly successful as they are produced naturally, which contains non-toxic and non-pyrogenic immunological adjuvants when mixed with conventional antigens for treating COVID-19 disease [40]. Hence, these pieces of evidence show that BSs play a huge role as immuno-suppressive agents and could be highly used as a combinational drug to relieve inflammatory responses caused due to SARS-CoV-2 infection.

Biosurfactants anti-viral activity against COVID-19

Certain BSs inactivates viruses due to physio-chemical reactions [41]. This hypothetical nature occurs only in enveloped viruses. Generally, it is stated that BSs disturb the viral membrane structures and disrupt the outer covering [27]. The hydrophilic nature of the BS occurs due to the presence of acetyl groups that promotes anti-viral activity [42]. Also, the hydrophobic nature with specific number of carbon atoms inactivates the virucidal effects [43]. High inactivation arises when the BS has a fatty acid chain with 15 carbon atoms and one negative charge; in addition, monomethyl esters showed viral inactivation in semliki forest virus [43]. The antiviral activity of BSs has been approved, and patents were obtained on treating various viruses [44–48]. Evidential reports from these studies can be applied in SARS-CoV-2 since it is an enveloped virus; hence, the mechanism of action has been explained as follows.

As the SARS-CoV-2 virus enters the host cell, the amphiphilic nature of BSs interacts with viral cell membrane and enters the bilayered lipid membrane that causes changes in permeability either by ion channel formation or disruption of the membrane system. A complete disintegration of the viral envelope and capsid protein occurs during high concentration of BSs. The disruptions of the lipid envelope and spike protein are encapsulated into micelles and results in viral inactivity. This micelle formation has the capability to function as liposomes that could deliver the drug to the infection site and also protects during hazardous conditions [49]. Hence, the nature of BSs to form as micelles would be an effective drug delivery system in treating SARS-CoV-2 infection. Also, BS does not affect the viral replication but inactivates the viral effects before adsorption or penetration. The mechanism of anti-viral activity by BS against SARS-CoV-2 is shown in Figure 2.

Recommendations

The COVID-19 disease, which is spreading vigorously, has become a global threat across the world. Discovery of any medicine or vaccine against this disease will be a kingmaker for the people suffering from this deadly infection. Hence, here we are recommending few products that will be produced using BS as a more potent way to get precautions or treatment from the

SARS-CoV-2 infection. The following are the guidelines:

- The BS has multi-purpose use in various fields such as food, pharmacology, cosmetics, detergents and so on. But its anti-inflammatory property would be a novel solution in targeting COVID-19 disease in multiple ways.
- As always, cleaning our hands will protect us from this virus. The strategy of using BS-encoded handwash or hand sanitizers promises to be a more protective shield against SARS-CoV-2 virus.
- The amphiphilic nature of the BS makes it easier to interact with SARS-CoV-2's lipid bilayer and would enable the destruction of the viral genome, which would facilitate easy clearance of the virus.
- The propensity of BSs towards drug delivery is high, especially because of its emulsification property.
- Hence, it is highly advisable that using or producing any drug from BSs along with conventional drugs or vaccines for COVID-19 will be beneficial because of its anti-viral and anti-inflammatory role against the SARS-CoV-2 virus.
- The list of clinical trials and ongoing trials about BSs as drugs against various respiratory disorders as well as for COVID-19 have been depicted in Table 2.
- As it is evident that BSs are eco-friendly and less toxic, it is recommended that its use in house-hold cleaning products or detergents will target and kill the SARS-CoV-2 virus.
- Another way of incorporating the BS in targeting the virus is its use as a medicated chewing gum.
- Incorporation of the BSs from microbes along with Indian medicinal plants promises to be highly instrumental in clearing the viral load efficiently from the human body.

Conclusion and future perspectives

Immunologists are working relentlessly to determine the immunity against SARS-CoV-2 and how long it may last [50]. Tremendous effort has been focused on neutralizing the antibodies, which bind to the viral proteins that directly prevent infection. Studies found that levels of neutralizing antibodies against SARS-CoV-2 remain high for a few weeks after infection but then typically begin to wane. Various therapeutic approaches have been recently discussed for COVID-19 [51]. Recently, there is an increased attention of BSs as therapeutic agents, due to their immunosuppressive potential and as a novel treatment molecule in most of the immune diseases. Scientists are working very hard for the best protection to the public before a vaccine is being made available [52]. Microorganisms can synthesize a high number of BSs at industrial scale, and these BSs from the microbial source could be a new move towards COVID-19; this kind of study is warranted at the current scenario to combat the pandemic situation.

Authors' contributions

Conceptualization — SMD, GV, VB; study design — SMD, GV, VB; investigation — SMD, MI, DV; resources and original manuscript writing — MI, DV, SS, AR, SK, AVG; review and editing — MI, AN, SK, AVG, RT; final approval — SMD, GV, VB, NSK.

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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 article.

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- * of special interest
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