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Review

The paradigm of prophylactic viral outbreaks measures by microbial biosurfactants

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ABSTRACT

The recent emergence and outbreak of the COVID-19 pandemic confirmed the incompetence of countries across the world to deal with a global public health emergency. Although the recent advent of vaccines is an important prophylactic measure, effective clinical therapy for SARS-Cov-2 is yet to be discovered. With the increasing mortality rate, research has been focused on understanding the pathogenic mechanism and clinical parameters to comprehend COVID-19 infection and propose new avenues for naturally occurring molecules with novel therapeutic properties to alleviate the current situation. In accordance with recent clinical studies and SARS-CoV-2 infection markers, cytokine storm and oxidative stress are entwined pathogenic processes in COVID-19 progression. Lately, Biosurfactants (BSs) have been studied as one of the most advanced biomolecules of microbial origin with anti-inflammatory, antioxidant, antiviral properties, antiadhesive, and antimicrobial properties. Therefore, this review inspects available literature and proposes biosurfactants with these properties to be encouraged for their extensive study in dealing with the current pandemic as new pharmaceutics in the prevention and control of viral spread, treating the symptoms developed after the incubation period through different therapeutic approaches and playing a potential drug delivery model.

Contents

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Introduction

Infectious viral diseases and outbreaks have indisputably emerged as a continuously evolving global threat. Today despite several advances made in medicine and research, the diagnosis and control of a viral outbreak continue to be a challenge due to their inherent attributes such as high genetic mutation. Coronavirus disease 2019 (COVID-19), an acute respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), initially appeared in Wuhan, central China, and was declared a global pandemic by WHO (World Health Organization) in early 2020 [1]. As of May 30, 2021 report, around 170 million people are affected by COVID-19, resulting in nearly 3.5 million deaths worldwide, affecting the global healthcare system and economic security [2]. The mortality rate corresponding to the ease at which viral infection is being transmitted through aerosol makes this strain of coronavirus so infectious [3]. Once infected, flu-like symptoms are induced in the patients becoming highly contagious with time course [4,5]. The infected host mostly relies on their immune system to combat SARS-CoV-2, complications in the immune response of patients due to underlying health conditions or co-morbidities lead to pneumonia or acute respiratory distress syndrome (ARDS) which can often be fatal [6].

SARS-CoV-2 is an enveloped, single-stranded RNA virus of approximately 26–32 kb genome size [7] belonging to the genus beta coronavirus, exhibiting swift transmission among humans leading to public health emergencies worldwide [8]. All coronaviruses encode four structural proteins: the spike protein (S), an envelope protein (E), a membrane protein (M), and a nucleocapsid protein (N) enclosing its genetic material (Fig. 1) [9,10]. SARS-CoV-2 infection into the host cell requires several conformational changes, involving the binding of spike protein to angiotensin-converting enzyme ACE-2 receptor on the host cell surface and fusion of viral envelope and cell membrane [8]. A successful binding, entry, and subsequent replication of an encapsulated virus inside the host cell consolidates several factors [8]. After the virus successfully enters the host, the innate immune system responds against it activating macrophage and dendritic cells using reactive oxygen species (ROS), reactive nitrogen species (RNS), and cytokines, which can cause inflammation and further aggravates the host immune response favoring COVID-19 progression [11].

Several collaborative scientific approaches are being coordinated globally for developing therapeutic and preventive solutions against COVID-19 including clinical trials of anti-inflammatory, antiviral, and anticoagulant treatment [12] and exploration of drugs with different targets effective in decimating SARS-CoV-2 are currently underway. Few of the approaches include targeting the lipid membrane or structural protein of SARS-CoV-2 as a possible alternative to kill the virus [13] and repurposed drug trials and combinatorial therapies are under investigation, with few of them believed to restrict the SARS-CoV-2 entry into the cytoplasm. Likewise, nafamostat mesylate, restricts the entry of coronavirus into human epithelial cells [14], there are also drugs, available for relieving the clinical symptoms of COVID-19 such as corticosteroids, ribavirin, azithromycin, lopinavir, metformin, doxycycline, favipiravir, galidesivir, cannabidiol, vitamin C and D, convalescent plasma, tissue plasminogen activator, interleukin-1 inhibitor, N-acetylcysteine calcifediol. Additionally, the dearth of specific therapy against COVID-19 infection has repurposed some of the drug therapies like remdesivier, ivermectin, chloroquine, and hydroxychloroquine against COVID-19 [17], although their clinical efficacy yet needs approval. The introduction of COVID-19 vaccines in the year 2021 marked a watershed moment in the global pandemic fight and by year-end, yet another milestone was achieved with the approval of two antiviral drug-molnupiravir and paxlovid reducing the mortality rate of COVID-19. However, the threat of viral resistance is particularly severe for these nanotherapeutic antivirals, targeting only one part of the virus. Therefore, it is imperative to develop new antiviral therapies geared at broad-spectrum specificity for coronaviruses and other respiratory viruses.

Recent research studies have described surfactant therapy as a considerate symbolic treatment against COVID-19 infection and mortality because of respiratory failure [18]. Exogenic surfactants have already been approved against neonatal respiratory disease syndrome and are also being used to treat COVID-19 infection [19]. Similarly, the use of microbially synthesized surfactants called biosurfactants has been suggested for its possible role in COVID-19 management because of their antiviral and anti-inflammatory properties. This mini-review emphasizes investigating the inference of oxidative stress versus cytokine storm-induced inflammation, concerning biosurfactants as an anti-inflammatory, antioxidant and anti-viral therapy in preventing fatal outcomes related to COVID-19. Biosurfactants are also investigated for drug delivery owing to their non-toxic, nonpyrogenic, and emulsification activity.

Biosurfactants (BSs)

Biosurfactants (BSs) are a structurally heterogeneous group of bioactive molecules exhibiting prominent surface and emulsification activity [20]. BSs are of biological origin predominantly synthesized from microorganisms and some plant species, making them less toxic and more biocompatible conferring their selective advantage over synthetic surfactants. They are mostly produced as secondary metabolites by different microorganisms including bacteria *(Bacillus, Pseudomonas, Mycobacterium, Actinobacteria, Nocardia, Arthrobacter*), yeast, and fungi (*Candida, Starmerella, Saccharomyces, Pseudozyma*) and plays an important role in the survival of microorganisms producing them either by interfering in host-microbe interaction or by acting as an antimicrobial agent [21].

These BSs are classified depending on their chemical structure, the producing microorganism, and their molecular mass and have been studied extensively for their biomedical significance (Table 1). BSs are amphipathic in nature with both hydrophilic (carbohydrate, cyclic peptide, amino acid, carboxylic acid, alcohol or phosphate) and hydrophobic (saturated, unsaturated, branched, linear fatty acids) moiety, which helps to reduce both the interfacial and surface tensions between two immiscible phases having a different degree of polarity and hydrogen bonding such as oil and water interphase.

These properties make BSs an excellent emulsifier, foaming, and dispersing agent. BSs acts on microbial cell surfaces by interacting with their cell membrane and instigating change in the surface energy, hydrophobicity reduction, and increasing the cell permeability. This causes membrane disruption and cell lysis, leading to metabolite leakage by modification of protein structure [30,35]. BSs have also been studied for safe oral, nasal, and dermal administration [36]. This elucidates the comprehensive use of BSs in therapeutics, environment, and industrial sectors to combat future viral outbreaks [37]. Several reports suggest the therapeutic application of BSs against viruses, inflammation, and immune disorders [38]. For instance, peptide and lipopeptide-type BSs disrupts the viral lifecycle, making them an ideal candidate for developing vaccines that induce cytotoxic T-cell response against viruses [7,39,40]. Peptidoglycan-associated surfactin BSs have been reported for their virucidal activity against several enveloped viruses including SARS-CoV-2. Similarly, Lipopeptide BSs such as surfactin produced by *Bacillus* sp. are known for their anti-inflammatory [41] and antioxidant response [42,43]. The anti-inflammatory properties of BSs [44] and natural antioxidant [45] for managing COVID-19 pathogenesis has been reviewed.

BSs, in addition, have an intriguing attribute, to form molecular aggregates, called micelles at their critical micelle concentration (CMC), which differs among different BSs classes. This micellar

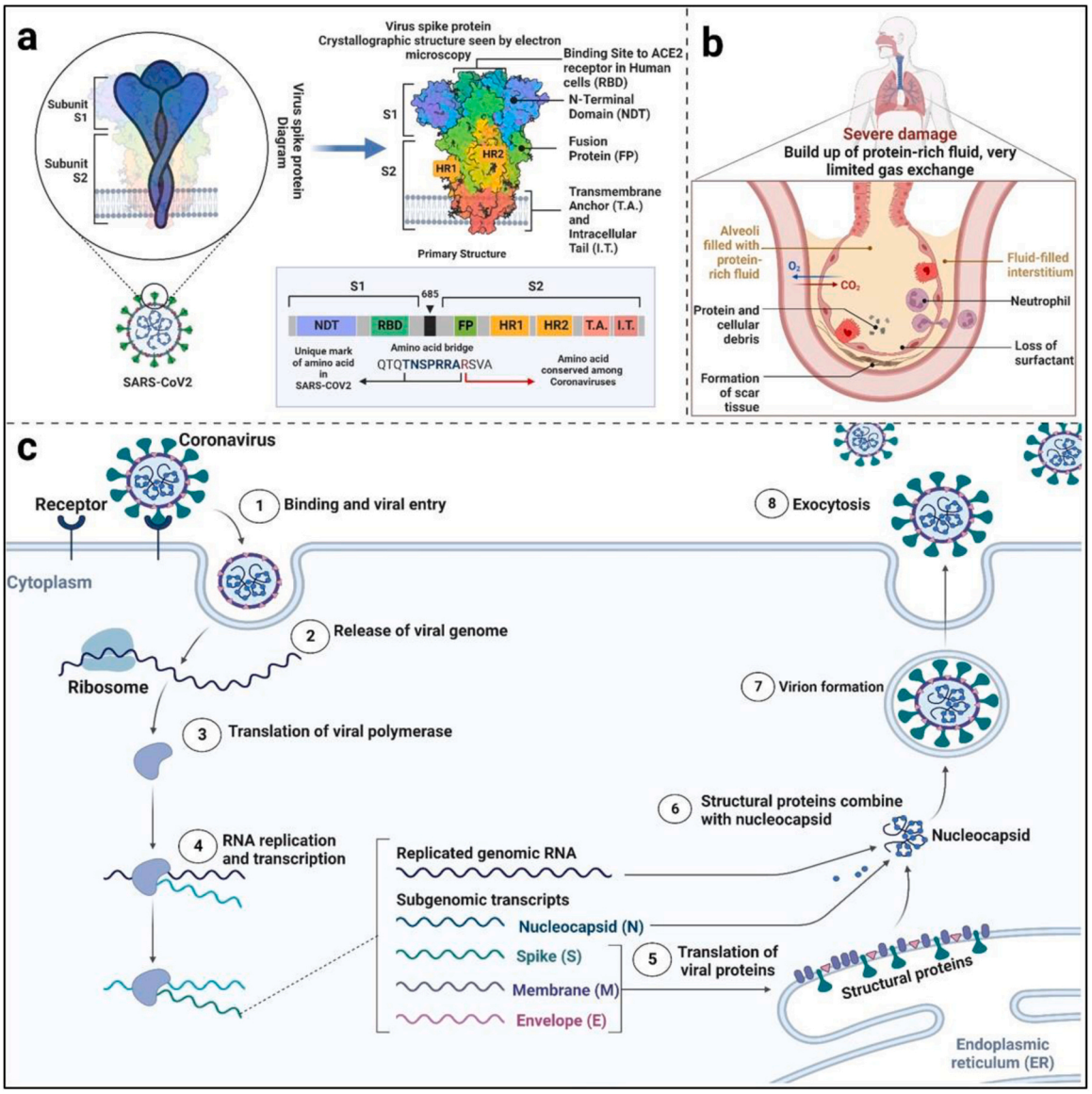

Fig. 1. Molecular pathogenesis induced by SARS-CoV infection. (**a)** An in-depth look into the structure of the SARS-CoV2 spike glycoprotein. (**b)** Severe effect of SARS-CoV2 on the human respiratory system. (**c)** Replication cycle of the coronavirus.

structure along with interacting and targeting the virus lipid membrane helps BSs in drug delivery applications [46]. This structure works as a liposome with micelles and emulsions delivering the drug to the site of infection without altering its activity [47]. These studies suggest the adaptability of BSs and their already large-scale existence in industries such as pharmaceutical and food, making them significantly important in finding a novel approach to deal with the COVID-19 pandemic [48] (Fig. 2).

Molecular pathogenesis of COVID-19: a cross-talk between pro-inflammatory cytokines and oxidative stress

COVID-19 disease severity and risk of mortality associated with variants of SARS-CoV-2 infection attributes to the development of respiratory and digestive tract injury [53]. The molecular level pathogenesis of the coronavirus has not been well studied and is still unclear, but growing shreds of evidence have suggested that the disease progression is related to immune-pathological mechanisms rather than viremia [54]. The activation of an efficient host immune response to fight against the viral infection is needed; however many of these immune effector cells may exacerbate damage during chronic disease and acute tissue injury [55]. The pathogenic mechanism of SARS-CoV-2 infection involves inflammatory and immune response signaling along with oxidative compounds such as reactive oxygen species (ROS) generated through oxidative stress [56](Fig. 3). In broad terms, SARS-CoV-2 infection stimulates the inflammatory response, which disrupts the redox homeostasis and induces oxidative stress, which helps maintain the inflammatory state, thus creating a vicious cycle. Hence, elucidating the molecular mechanism involved in disease pathophysiology could be crucial in understanding and developing novel therapeutic strategies against SARS-CoV-2 infection.

Data from previous studies with SARS-CoV and MERS-CoV supports a better understanding of SARS-CoV-2 pathogenesis; however, it is still under construction. The SARS-CoV-2 enters the target cell by binding to the receptor of angiotensin 1 converting enzyme ACE-2 through spike glycoprotein (S-protein) (118). ACE-2 is a dipeptidyl carboxypeptidase in the RAS system that hydrolyzes angiotensin (Ang) II a vasoconstrictor into Ang (1–7) a strong vasodilator [57,58]. Very recently, ACE2 has gained attention as a functional receptor for SARS-CoV and SARS-CoV-2 infection and pathogenesis [59]. The SARS-CoV-2 Spike glycoprotein is composed of two subunits S1 and

Table 1
Classification of Biosurfactants, and their role in various potential medical applications.

Biosurfactants		Microorganism	Potential medical applications	Reference
Group	Class			
Glycolipids	Rhamnolipids	*Pseudomonas aeruginosa, Pseudomonas chlororaphis, Pseudomonas fluorescens, Pseudomonas luteola, Pseudomonas putida, Pseudomonas stutzeri, Burkholderia glumae, Burkholderia plantarii, Burkholderia kururiensis, Burkholderia Pseudomallei, Streptococcus mutans, Streptococcus oralis, Streptococcus sanguinis, Neisseria mucosa, Actinomyces naeslundii*	Anti-microbial activity, cytotoxic activity	[22–25]
	Sophorolipids	*Torulopsisbombicola, Candida bombicola, Rhodotorulabogoriensis, Candida albicans, Candida glabrata*	Anti-viral, anti-microbial, anti-inflammatory and antifungal activity	[26–29]
	Mannosylerythritol lipids	*Pseudozyma antarctica, Ustilagomaydis*	Anti-microbial activity, anti-oxidant activity, immunological and neurological property	[30–32]
	Trehalolipids	*Rhodococcus erythropolis, Nocardia erythropolis, Mycobacterium* sp., *Arthobacter* sp., *Corynebacterium* sp.	Anti-viral activity against herpes simplex virus and influenza virus	[32]
Lipoprotein	Surfactins/viscosin	*Bacillus subtilis, Bacillus licheniformis, Pseudomonas libanensis, Pseudomonas fluorescens*	Anti-coagulant, anti-mycoplasma, anti-viral, antibacterial, anti-inflammatory	[33,34]

S2, contributing to the pathogenesis of SARS-CoV-2 by receptor recognition and cell membrane fusion [59]. Also, the S1 subunit has the receptor-binding domain, which binds to ACE2, of RAS found on alveolar epithelial type II as a functional virus receptor [60]. The binding of SARS-CoV-2 to ACE2 receptor damages the type II alveolar cells reducing the pulmonary surfactant present in the alveolar space, the surfactant exhaustion thus results in atelectasis and acute respiratory distress syndrome (ARDS) [60]. In contrast, the S2 subunit of spike protein catalyzes membrane fusion releasing the genetic material inside the cell. It also has non-structural protein which helps in RNA processing and replication [60] thus triggering the host immune response to combat the infection through toll-like receptors (TLRs) which activates the nuclear factor kappa-B (NF-kβ) pathway, initiating inflammatory response as part of host immunity [61]. NF-kβ pathway produces pro-inflammatory cytokines recruiting more immune cells, increasing cytokine production (Interferon (IFN)γ, tumor necrosis factor (TNF)-α, interleukin (IL)− 1, IL-6, and IL-18) and resulting in a cytokine storm, which leads to the worst prognosis of the infected host [62]. There is strong evidence that cytokine storm may play a role in COVID-19 pathogenesis, similar to previous epidemics such as SARS-CoV, and MERS-CoV [63]. Also, the activation of the NF-kβ pathway catalyzes the transcription of pro-IL-1b and procaspase-1 in the nucleus, and in the presence of additional signals like ROS or multiprotein complex inflammosome, the pro-IL-1b is cleaved by pro-inflammatory protease caspase 1 to mature IL-1b (B. (Costela-Ruiz et al., 2020).). This leads to cytokine production such as (TNF-α, IL-1B, IL-6, and IL-2) and cytokine storm resulting in necrosis and cell death [44]. The inflammasome is formed by activation of NOD-like receptor protein (NLRP3), an innate immune response system with pathogen-associated molecular pattern (PAMPs) and damage-associated molecular patterns (DAMPs) sensor upon SARS-CoV-2 infection [64,65]. The NLRP3 inflammasome leads to cell death via apoptosis and pyroptosis, an inflammatory programmed cell death that releases several pro-inflammatory mediators [65,66].

While SARS-CoV-2-induced lung and other tissue damage are most likely the results of multifactorial mechanisms, recent studies have suggested a possibility of oxidative stress playing a major role in the progression of inflammatory response and organ dysfunction [67,68]. The infection of SARS-CoV and SARS-CoV-2 has been reported in ACE2 shedding and subsequent downregulation of surface ACE2 expression [61]. The downregulation of ACE2 by endocytosed SARS-CoV-2 increases the Ang II plasma concentration and initiates binding of Ang II to AT1R (Angiotensin type 1 receptor), activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX), an important determinant for ROS generation [69]. ROS triggers the NLRP3 inflammasome induction. Although there have been several pathological pathways reported for NLRP3 inflammasome induction [70], oxidative stress activates the NLRP3 inflammasome via the NF-kB pathway and thioredoxin protein activation [71,72]. In addition, the NF-kB pathway upregulates a surge of pro-inflammatory factors such as (IL-18, and IL-1beta), further increasing NLRP3 inflammasome induction. This high reactivation of NLRP3 inflammasome mounts pyroptosis [17] and host cell and organ damage [73]. The underlying molecular mechanism of SARS-CoV-2 infection, inducing inflammation and oxidative stress in COVID-19 pathogenesis are summarized in (Fig. 4).

Biosurfactants: approach toward prevention and management of pandemic

BSs can be useful to different health sectors as an innovative and alternative sustainable approach in prevention and management of the outbreak. These comprises the uses of BSs in therapeutics (anti-inflammatory action, anti-virus, drug delivery system and immune system enhancers), different industrial sectors such as disinfectants, surface cleaning agent and detergent.

Therapeutics

Interrupting the transmission cycle thereby obstructing the spread of a pathogen is the most important step in fighting an outbreak. This necessitates effective treatment and drug development against the disease. However, the required clinical trials and approval for a drug development take years. Therefore, the use of already approved or repurposing existing drugs in targeting a new pathogen can contribute towards an innovative and effective therapy in shorter duration. The distinctive molecular features of BSs make them a promising biomolecule in pharmaceutical industries [26]. BSs, for safe oral, nasal and dermal administration has been reported [27].

BSs acts on the microbial cell surfaces by interacting with their cell membrane and instigating change in the surface energy, hydrophobicity reduction and increasing the cell permeability. This therefore causes membrane disruption and cell lysis, leading to metabolite leakage by modification of protein structure [24,74]. The most common BSs studied for pharmaceutical applications include

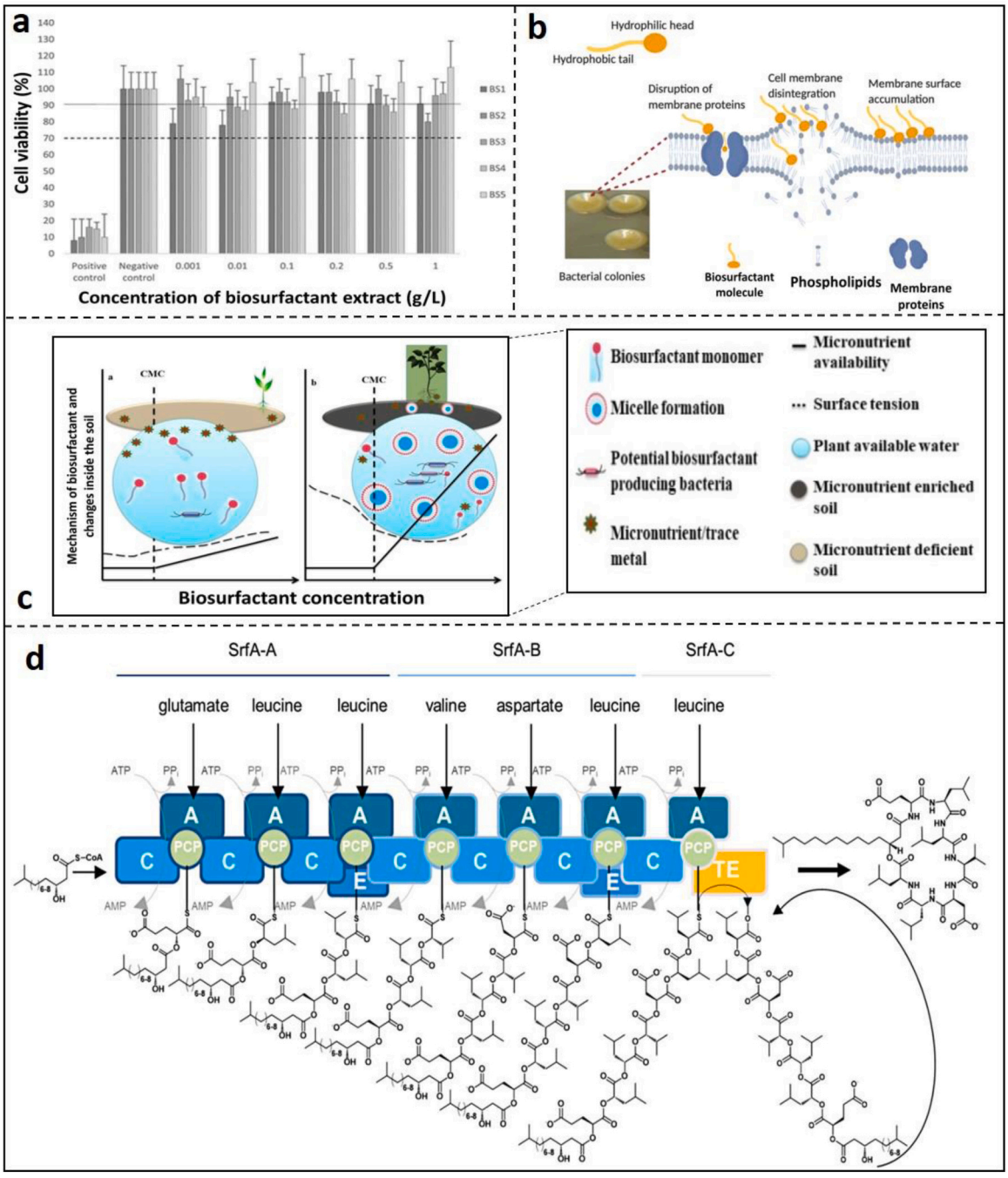

Fig. 2. (**a).** Cell viability detected in mouse fibroblast cells (NCTC clone 929) in the presence of different concentrations (g/L) of BS1, BS2, BS3, BS4, and BS5, compared to the positive control (phenol) and negative control (DMEM, 0 g/L biosurfactants). (**b)** Theoretical interactions between biosurfactant molecules and bacterial cells. Primary mechanisms; disruption of cell membrane and proteins responsible for the essential function. (**c).** Impact of micronutrient deficiency on plant growth and soil quality on a micronutrient-deficient soil. Mechanisms of biosurfactant application enhancing micronutrient availability in micronutrient-deficient soil to the plant, soil quality, and related water quality through increasing nutrient solubility at a fixed concentration of biosurfactant molecule. C.M.C. at which there is a sudden increase in metal solubility in the system. (**d).** Biosynthetic pathway of lipopeptide surfactin through non-ribosomal peptide synthetases (NRPSs) including surfactin synthetase complex with four enzymatic subunits including SrfA-A, SrfA-B, and SrfA-C.
(a) The dotted line indicated the limit (70%) of cytotoxicity according to UNE-EN-ISO 10993–5 standard, whereas the solid line marked 90% of cell viability, indicating mild cytotoxicity (Image adapted from [49]). (b) A, C, E, PCP, and TE represent adenylation, condensation, epimerization, peptidyl carrier, and thioesterase domains, respectively (Image adapted from [52]). (c) (Image adapted and modified from [50]). (d) (Image adapted and modified from [51]).

lipopeptides, mannosylerythritol lipid and glycolipid from Candida species. They have proven their efficacy in different sectors, such as, a potent drug delivery and an antimicrobial agent. Low toxicity and biocompatibility confers their selective advantage over synthetic surfactants efficacy. In recent years, several studies have pointed BSs and its innovative applications to be exploitable for effective therapeutic development.

Anti-inflammatory potential of biosurfactant

The multifunctional interaction of BSs with biological systems leads to several biochemical and physiological activities. BSs have been well known to initiate anti-inflammation against pathogenic infection in humans [75]. Recent research reports BSs surfactin mediated reduction of lipopolysaccharide (LPS)-stimulated

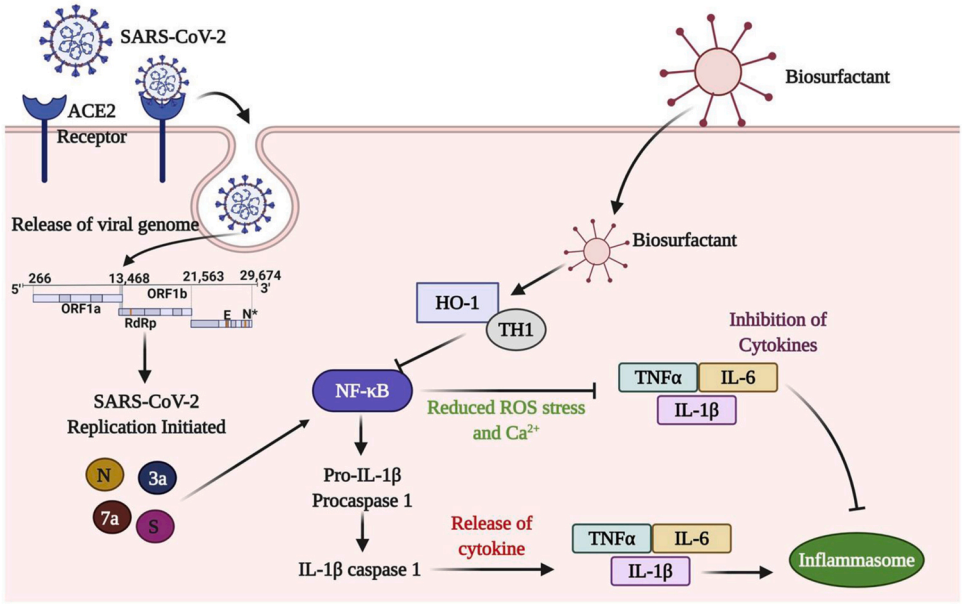

Fig. 3. Anti-inflammatory role of biosurfactants (BSs) against COVID-19: The above image depicts the hypothetical role of BSs as anti-inflammatory agents against COVID-19. When the SARS-CoV-2 enters the cell, it binds to the ACE2 receptor following which the TMPRSS2 helps in the cleavage of the S protein into S1 and S2 subunits. Subsequently, the viral replication gets initiated resulting in the NF-κB pathway, which stimulates the release of the cytokine storm. In this condition, providing 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.

macrophage function, IL-2 expression, and TLR4 protein expression, inducing anti-inflammatory effect [45]. Different Phospholipase A2 (PLA2) collectively known as cytosolic phospholipase (cPLA2) secretes arachidonic acid (AA), which acts as a precursor for eicosanoids production, maintaining inflammatory response [76]. The structural attribute of BSs are identified by toll-like receptors (TLR-2), and communicate with the cell membrane, inhibiting cPLA2 and inducing an anti-inflammatory response [45].

Consistent with these results, surfactin has been reported to exert an anti-inflammatory effect by blocking the degradation of nuclear factor kappa-B kinase subunit beta (IKK-β), a cytoplasmic suppressor of the NF-kβ signaling pathway, which is responsible for pro-inflammatory cytokine production [45]. Surfactin has been proven to be an anti-inflammatory and neuroprotective agent [77]. Similarly, BSs sophorolipid from yeast has been shown to have potent anti-inflammatory and immunomodulatory properties against chronic inflammatory conditions [78]. Along with cytokine storm, a recent study involving COVID-19 patients reported enhanced production of cellular heme and inhibition of biliverdin, ferrous iron, and carbon monoxide, inducing stress and inflammation in SARS-CoV-2 viral infection [79]. The surfactin from *Staphylococcus aureus* induced an anti-inflammatory effect by obstructing the lipoteichoic

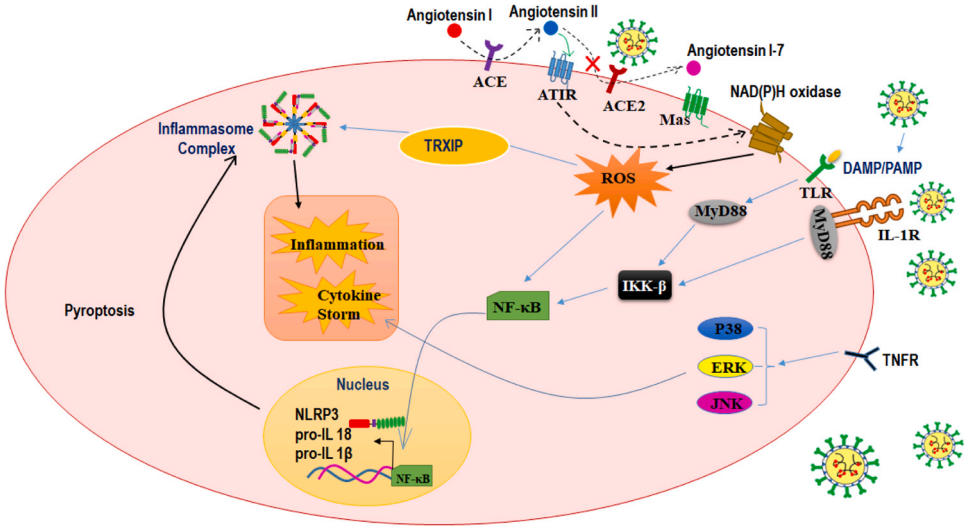

Fig. 4. Molecular pathogenesis induced by SARS-CoV infection. SARS-CoV-2 can bind to receptors such as host alveolar epithelial cells or immune cells and mediate inflammatory cascade, activating inflammosome complex and illing the host cells. The virus activates immune host cells such as macrophages and monocytes directly or indirectly, contributing in host immune response causing inflammation and cytokine storm. On the other hand, Ang II binds to AT1R receptor and contributes in ROS production through NAD(P)H dependent mechanism. ACE2: Angiotensin converting enzyme 2, TNFR: Tumor Necrosis Factor, TLR: Toll Like Receptor, IL-R: Interleukin Receptor, AT1R: Angiotensin type 1 receptor, NAD(P)H oxidase: Nicotinamide adenine dinucleotide phosphate oxidase, ROS: Reactive oxygen species, MyD88: Myeloid differentiation primary response 88, NLRP3: Nod like receptor protein 3, TRXIP: Thioredoxin interacting/inhibiting protein, NF-kB: Nuclear factor-kB, ERK: Extracellular signal activated kinase, JNK: c-Jun N terminal kinase.

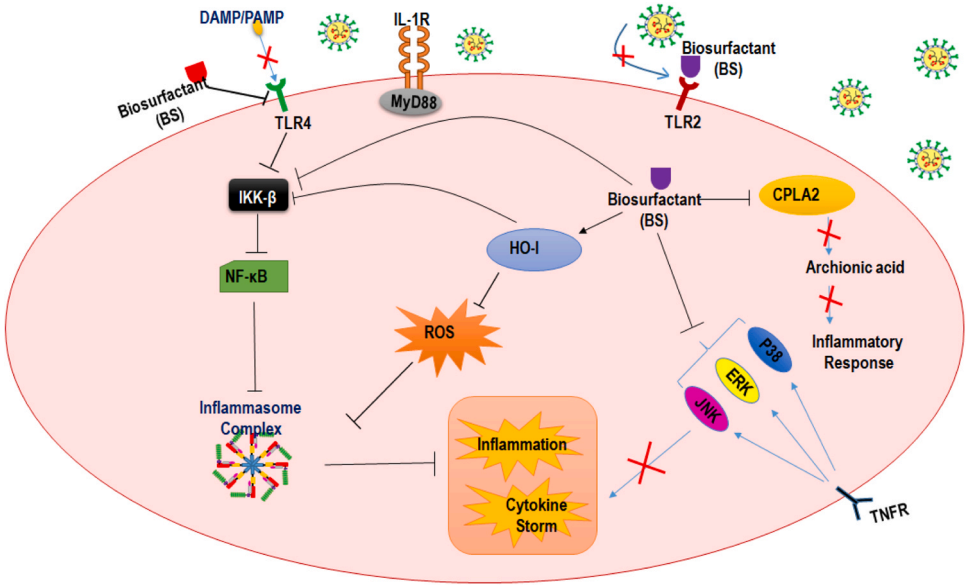

Fig. 5. Anti-inflammatory activity of BSs against SARS-CoV-2. The figure depicts the hypothetical role of BSs as an anti-inflammatory agent against COVID-19 infection. BSs can inhibit the production of pro-inflammatory mediators by impeding the pathways triggered by TLR, IL-R and TNFα-R. This can inhibit NF-Kb, p38, ERK and JNK signaling pathways. BSs can also trigger HO-1 synthesis and inhibit ROS generation and subsequent cytokine storm formation. TNFR: Tumor Necrosis Factor Receptor, TLR: Toll Like Receptor, IL-R: Interleukin Receptor, ROS: Reactive oxygen species, MyD88: Myeloid differentiation primary response 88, NF-kB: Nuclear factor-kB, ERK: Extracellular signal activated kinase, JNK: c-Jun N terminal kinase, HO-1: Heme oxygenase, cPLA2: Cytosolic phospholipase 2.

acid (LTA) induced signaling pathway, suppressing NF-k activation and subsequently activating hemeoxygenase (HO-1) orchestrated anti-inflammatory and antioxidant effect [77].

Similarly, BSs reduced the production of the pro-inflammatory cytokines in *P. gingivalis* LPS-stimulated THP-1 human macrophage cells by expressing the heme-oxygenase-1 enzyme [80]. Although so far there is no evidence for targeting HO-1 against SARS-CoV-2 infection, it has been suggested that inducing the expression of the HO-1 enzyme may avert SARS-CoV-2 complications through anti-inflammatory and antiviral properties [80]. These studies reveal the anti-inflammatory activity of BSs, suggesting their potential as a therapeutic candidate in the treatment of inflammatory diseases. Hence, BSs could be proposed as a feasible way to reduce the repercussions of cytokine storms caused by SARS-CoV-2 infection. Hence, the proposed hypothetical mechanism of BSs-induced anti-inflammatory activity includes interference of BSs with pathways induced by Toll-like receptor (TLR), interleukin-1 receptor (IL-1R), and Tumor necrosis factor-α (TNF- α) receptor.

BSs anti-inflammatory activity also includes cytosolic phospholipase A2 (cPLA2) interaction and inhibition of anti-inflammatory responses. In addition, administrating BSs to COVID-19 patients could inhibit the NF-kβ signaling pathway, activating the HO-1 enzyme, catalyzing down-regulation in oxidative degradation of heme into biliverdin, ferrous iron, and carbon monoxide, and protects the body against oxidative stress and inflammatory activity. The hypothesized anti-inflammatory mechanism of BSs mediating anti-inflammatory activity against SARS-CoV-2 infection is summarized in (Fig. 5).

Therapeutic potential of BSs antioxidants

As mentioned before, oxidative stress plays a significant role in SARS-CoV-2-induced apoptosis and pathogenesis. Oxidative stress is the discrepancy between oxidants and antioxidant production, leading to the deregulation or interruption of the redox signaling system [81,82,83]. To counterbalance the oxidant species such as ROS and reactive nitrogen species (RNS), enzymatic and non-enzymatic molecules synthesize an antioxidant species [84,85]. However, during viral infection the antioxidant system such as superoxide dismutase (SOD) and catalase (CAT) get affected, reducing the level of antioxidants such as (ascorbic acid, carotenoids, glutathione) and thereby increasing the oxidative stress [86,87] [88].

Therefore, investigating natural compounds with antioxidant potential as a therapeutic approach, as either a substitute or an adjuvant to existing conventional therapies can ameliorate the consequences of coronavirus infection.

Antioxidants counteract ROS production during oxidative stress and improve the disease condition via different mechanisms [89,90]. They either directly convert the ROS into inactive form by converting hydrogen peroxide to water and oxygen or donate hydrogen to free radicals, thus scavenging the free radicals [91,92,89,93]. Antioxidant flavonoids such as curcumin, sulforapphone, quercetin, berberine, luteolin, and catechin widely present in fruits, vegetables certain beverages, and spices are reported to inhibit ROS accumulation and cell apoptosis in coronavirus, gastroenteritis coronavirus and porcine epidemic diarrhea coronavirus [94,95]. Besides this, some natural antioxidants exhibit efficient antiviral activity against COVID-19 infection by disrupting SARS-CoV-2 replication targets. For example, isobavachalcone and psoralidin were reported to inhibit SARS-CoV-2 papain-like protease (PLpro) [96].

Among the plethora of natural agents with antioxidant activity (Table 2) studied for their effectiveness against coronavirus infection, there is also a group of natural compounds called carotenoids. Carotenoids are a group of phytochemicals synthesized by plants and microorganisms exhibiting pharmaceutical benefits such as anti-inflammatory, antiviral and anticancer. There have been several reports proposing the therapeutic potential of carotenoids in combating the emergence of COVID-19 [97]. For example, lycopene is proposed to reduce oxidative stress-induced diseases like cancer, neurodegenerative disorder as well as viral infection and also possesses anti-inflammatory properties [98]. Lately, there have been several reports exploring BSs from different sources, bestowed with excellent antioxidant properties [99]. In addition, another report has assessed the BSs as a natural product, capable of blocking the oxidative chain, impeding ROS and RNS elevation by rendering antioxidant activity, hence being a useful therapeutic molecule [100].

Table 2
Natural antioxidants tested against coronavirus infection in in vitro models and their antiviral effects.

Antioxidant	Type of cells tested	Antiviral effect	Reference
Quercetin, Epigallocatechin gallate, Gallocatechin gallate	Recombinant 3 CLpro was expressed in pichiapastoris GS115	Inhibition of coronavirus replication	[103]
Amentoflavone, Rhoifolin, Apigenin, Luteolin, Quercetin, Herbacetin, Pectolinarin	SARS-CoV 3 CLpro inhibition using fluorescence resonance energy transfer analysis, molecular docking and mutagenesis	Inhibition of SARS-CoV replication	[42,104]
Catechin	TGEV infected ST cells	Inhibition of TGEV induced apoptosis	[105]
Quercetin 7- rhamnoside (Q7R)	PDEV infected Vero cells	Reduction of cytopathic effect (CPE) without fragmenting DNA	[94]
Resveratrol	MERS- infected VeroE6 cells	Inhibition of MERS induced apoptosis	[106]
Herbacetin, Isobavachalcone	Tryptophan based fluorescence method	Inhibiton of MERS-CoV replication	[107]
Myricetin, Scutellarein	SPR/FRET-based bioassays	Inhibition of SARS-CoV replication	[108]

The BSs MB15 from non-pathogenic marine bacteria was studied to have a potent antioxidant, antimicrobial, and non-cytotoxic effect [101]. Likewise, BSs isolated from *Bacillus* sp. were reported for their antioxidant and antiadhesive property [99,102]. Collectively, knowing the therapeutic potential of BSs and antioxidants independently, we would like to propose the significant potential of BSs antioxidants for the treatment and prevention of COVID-19.

Biosurfactants as a potent antiviral molecule

Currently, a concrete explanation for microbial BSs production is unknown, however, a likely explanation can be offered by tracing back the evolutionary analyses. BSs production has often been experienced within the species thriving in a depleted resource ecosystem. This explains their competitive advantage in defense, resource acquisition, and survivability over the organisms that are not able to produce BSs [109,110]. BSs are known to alter the viral membrane structures and disrupt their outer covering [111], the acetyl groups and the carbon chains in BSs providing the hydrophilic and hydrophobic nature have been stated to promote antiviral activity [112,113]. Moreover, previous studies have shown the defensive nature of BSs to inactivate the viral envelope through bioactive peptides. A bioactive peptide cyclosporine A (CsA) from the fungus *Tolypocladium inflatum* is known to hinder influenza virus dissemination by meddling with their life cycle [114,115]. This biopeptide inhibits the steps after protein synthesis like assembly or budding [115], which is exceptionally important because budding aids in viral exit from host cells, attaching to the derived membranes enriched in viral proteins reassuring their spread and infection [116]. By triggering the final stage of the virus's lifecycle, the challenge with current drug resistance can be countered, preventing the spread in cases such as the current COVID-19 pandemic [117]. A microbial glycolipid, Sophorolipids (SLs) have been explored for their antiviral activity against human HIV, Epstein-Barr, and Influenza virus [118]. Also, the acetylation and modification in SLs are reported to improve the hydrophilicity of SLs and promote their antiviral and cytokine-stimulating properties against herpes and HIV virus [119]. Interestingly, these studies have shown the inactivation of enveloped virus because of BSs physio chemical reactions [6], which further point towards the potential of BSs as an antiviral agent against enveloped SARS-CoV-2. Although, the exact mechanism of BSs as an antiviral is unknown, but it has been hypothesized that the BSs interact with the cell membrane and change the membrane permeability by either membrane solubilization or ion channel formation [6]. Disruption and encapsulation of viral envelope and spike protein into the micelles formed when BSs concentration increases play an important role in viral inactivity [47]. However, in-vitro studies are required for the screening of potent BSs molecules against SARS-CoV-2.

Biosurfactant mediated vaccines and immunity

With Covid-19 infection, a healthy immune system entirely eradicates the virus without the patient displaying any symptoms. By inducing or activating immune cells such as macrophage, neutrophils, B cells and T cells, which deals with the production and memory storage of viral specific antibodies for recurrent infections, an effective adaptive immune response can be produced [120]. For example, inducing T cells facilitate the differentiation B cells into memory cells and plasma cells producing viral specific antibodies for recurrent infections [121]. Therefore, T cell activation through adaptive immunity contributes significantly to the prevention of new infection. Administration of vaccine is one of the reliable mode of activating T cells. When compared to whole cell or protein vaccines, peptide antigens may be produced at high purity, which makes them a more potent vaccine. Low immunogenicity, however, places them at a disadvantage.

In parallel, BSs such as lipopeptides (of varied structure) have been reported as a non-pyrogenic, nontoxic and an effective immunological adjuvant for antigenic priming and designing vaccines, which activates the immune system via toll like receptor (TLR2) signaling [122]. In order to combat various viral infection, lipopeptides adjuvants can stimulate the cytotoxic T lymphocytes (viral specific) by recognizing viral peptides coupled with major histocompatibility complex (MHC) class 1. A synthetic viral peptide, covalently attached to Tripalmitoyl-S-glycerylcysteinyl-seryl-serine lipopeptide has been reported to elicit cytotoxic T cell based immunological response [37]. Such preparations can be used as a stock to improve immunity when combined with further medication or are highly effective in situations when a primary immunity against a virus is lacking. However, employing efficient formulations combined with adjuvants that can boost immunity with utmost safety and efficacy is proving to be a major challenge for vaccine development [123]. Some of the studies reported earlier revealed role of BSs along with bioactive peptides for inactivation of encapsulated viruses. For example, the biopeptide cyclosporine A, produced by the fungus *Tolypocladium inflatum*, apparently impeded the influenza viruses' life cycle by preventing or delaying viral assembly following the synthesis of protein [120]. It was formerly thought that focusing on viral life cycle may be helpful in addressing antiviral drug resistance thereby liming the disease propagation.

Biosurfactants as a precautionary intervention for sanitization

Since the start of Covid-19 pandemic, the stress on importance of personal hygiene and cleaning has seen a dramatic increase in products such as mask, gloves, disinfectants, soaps and hand sanitizer. Anionic surfactants are surface-active agents used for cleaning products and detergents and accounts for 15–40% of total detergent composition [119]. The mechanism by which soaps or detergents acts to kill the microorganisms when applied to the surface depends

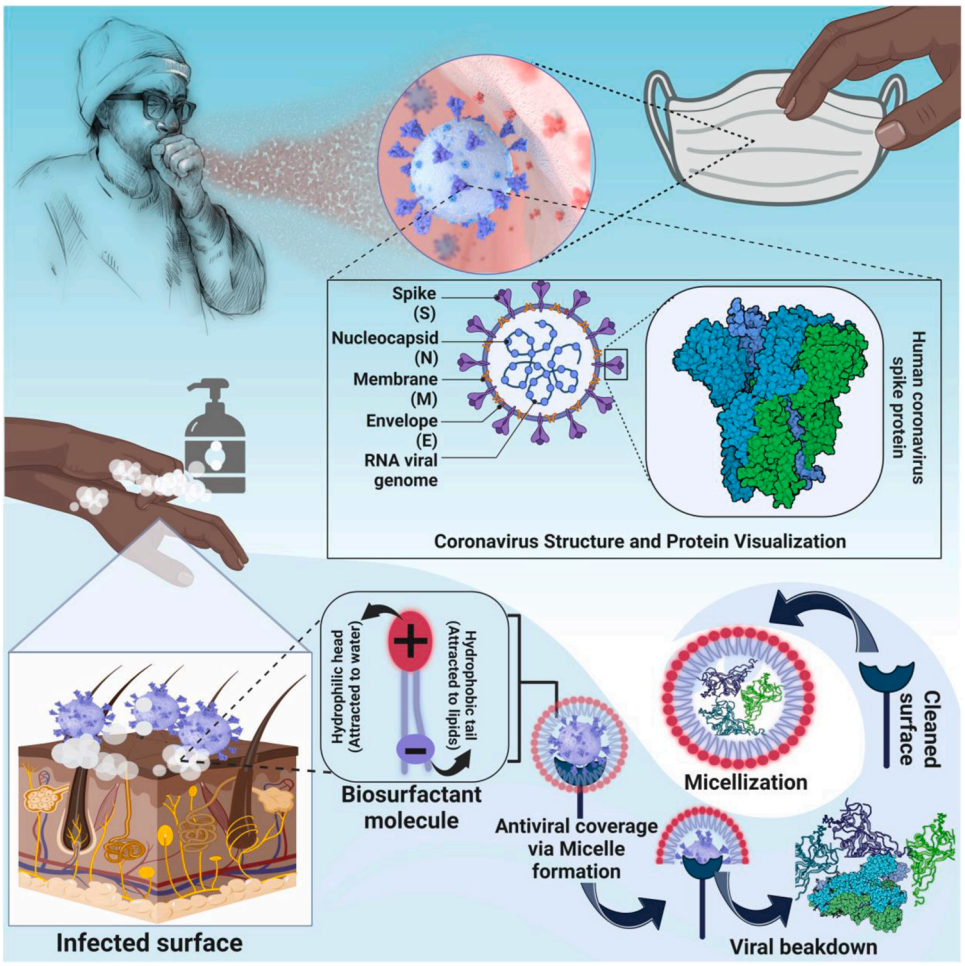

Fig. 6. Sustainable SARS COV-2 removal from environmental surfaces using biosurfactants.

on their fatty acid chain, which binds to the hydrophobic domain of microorganisms, and simultaneously surfactants hydrophilic part binds to water solubilizing the microorganism (Fig. 6). Therefore, this emulsification response aids in surface cleansing and at the same time depositing an active surfactant layer on the surface. Once attached, the electric charge on the surfactant molecules solubilize the harmful dirt particles and microbes into smaller droplets resulting in their emulsification. When the surfactant molecules are uninterruptedly attached to dirt particles and microbes, repulsion continues averting the same particle from being reintroduced to the surface [119]. One of the most common surfactant used for detergents and soaps are linear alkyl benzene sulfonates (LAS) [6]. These chemical surfactants however are emerging as one of the persistent contaminant and threat to environment. The harmful effect these surfactants leave on the living organisms and their ecosystems are well reported [124].

BSs serves to be of great benefit over the synthetic surfactants because of their low toxicity, eco-friendly nature and biocompatibility to humans [20]. Several microbial BSs are already commercialized and are present in the market as household detergents and essential ingredient in cosmetic and personal care products [125]. For example, companies such as Saraya, Henkel and Ecover for their laundry and cleaning products use sophorolipids while companies like Unilever, BASF, Evonik, and TeeGene commercializes products based on BSs such as lipopeptide and rhamnolipids [126]. Therefore, using products with BSs in concurrence with or as an alternative to chemically synthesized cleaning products may play a more effective role in disinfection.

Along with routine practicing of using soaps for hand wash, WHO has also endorsed the use of alcohol based hand sanitizers when handwashing facilities are not readily available. However, the efficacy of hand sanitizers when compared to soap and water has been a constant source of debate. The key component of sanitizers such as alcohol and isopropyl alcohol are highly toxic to water bodies when spill in aquatic environment and their repeated and prolonged use can cause skin damage, and risks the ability of skin to fight against other viruses and microorganisms [127]. Excessive usage of alcohol-based hand sanitizers for hospital equipment's and settings are reported to create selection pressure, developing more resistant pathogenic strains [128]. Several comparisons have been made between the efficacy of hand soaps and hand sanitizers and according to the Center for disease control and prevention (CDC); soaps serve to be more effective than hand sanitizers [129]. Nevertheless, the devastating impact of soaps, chemical surfactants and alcohol on human health and environment could not be ignored due to their unrestricted use amid Covid-19. Therefore, there is a direct need to replace them with nontoxic and ecofriendly biosurfactant based hand wash and sanitizers.

Biosurfactants as drug delivery system

Drug delivery systems are designed to improve the effectiveness of drug and when considering the drug delivery system for SARS-CoV-2 infection, it is important to choose a mode of drug delivery that not only protects the molecular nature of the drug but also successfully deliver it to the area of interest. However, poor drug

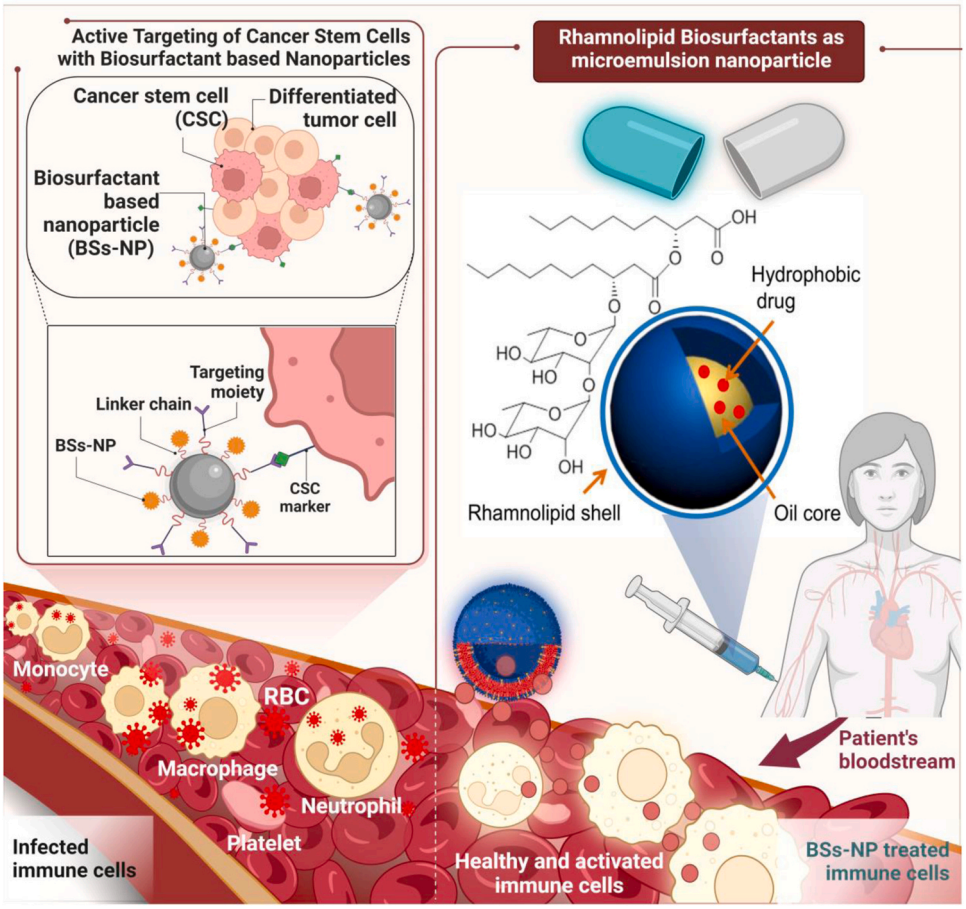

Fig. 7. Schematic diagram presenting the role BSs in cancer therapeutics, along with the mechanism of rhamnolipid BSs as microemulsion nanoparticle stabilizers for drug delivery.
(Image adapted and modified from [132]).

delivery because of drug precipitation and dilution are among the main challenges faced in designing the system. The self-aggregating characteristic of BSs to form a micelle-like structure makes them a potential candidate to design the drug delivery system. The micellar structure can form a stable liposome encapsulating the hydrophobic and hydrophilic drug in the emulsion protecting them from damage [130]. Glycolipid BSs micellar structure is known to form stable liposomes, niosomes, and cubosomes serving as a drug delivery vehicle to the infection site, maintaining the molecular structure of the drug inside the body fluid environment [110]. The higher solubility, bioavailability, biocompatibility, and thermodynamic stability of BSs-based microemulsion drug delivery systems can make the already prevailing therapeutics more efficient and effective. BSs such as glycolipid and lipopeptides have been used as a possible replacement for the already prevailing synthetic delivery system [131].

With SARS-CoV predominantly having a virulence effect on the respiratory and gastrointestinal tract, an aerosol formulation with BSs drug delivery system is considered as a likely mode of the delivery system. The self-solubilizing property of BSs promotes pharmacological dosage proportionality, resulting in more uniform effects across the patients [112]. BSs along with the safe passage of the drug to its target provides natural anti-viral property to the infection site and relieve surfactant dysfunction in the alveoli, another consequence of SARS-CoV infection. Clinically approved BSs, when consumed in gummies or lozenges are reported to directly reach the mouth and esophagus providing symptomatic relief [125]. In addition to this, Rhamnolipid BSs as microemulsion nanoparticle stabilizers for drug delivery have also been reported [37] (Fig. 7). Therefore, this suggests the potential of BSs-based drug delivery system that can be explored for their potential use in SARS-CoV infection.

Conclusion

The emergence of the COVID-19 pandemic has posed unparalleled challenges to public health, impeding our society's natural functioning and affecting the economy and public well-being across the globe. Outbreak management and preparedness involve an integrated approach comprising several applications to be applied simultaneously against the infection [15]. Scientists from all over the world have been working relentlessly to find ways to combat the pandemic [16] and therapeutic approaches have lately been discussed for COVID-19 [17]. Recently, the use of sustainable BSs synthesized from microorganisms can be an ideal approach to COVID-19; this sort of research is warranted to combat outbreak emergencies. In addition to this, BSs are compatible to be used for future technology such as nanobiotechnology and successful drug delivery system. Besides, BSs have gained wide attention from the scientific community to exhibit high therapeutic properties to be included in immunomodulatory, anti-cancer, anti-viral, wound healing, and the treatment of SARS-CoV infection, particularly in the alleviation of symptoms related to ARDS. However, substantial future research is needed to understand the way BSs works in combating the pandemic. One of the fundamental barriers that should be the focus of future study is the high production cost involved with BSs production during the down-streaming process. Reduced bioprocessing

costs along with persistent research on BSs application in this sector are important in outbreak emergencies such as COVID-19. The adaptability found across BSs structure and function justifies their use and application discussed so far. As research in this field advances, the practice and socioeconomic development of BSs will increase. As already, the world has suffered and still suffering the detrimental effect of the pandemic it is important to look forward to new approaches to combat any future consequences. In this way, the implementation of BSs provides an opportunity not only to face the challenges of the current pandemic but also to be better equipped for the future.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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