Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Review article

Theranostic efficiency of biosurfactants against COVID-19 and similar viruses - A review

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ABSTRACT

The world has witnessed an extreme vulnerability of a pandemic during 2020; originated from China. The coronavirus disease 2019 (COVID-19) is infecting and beginning deaths in thousands to millions, creating of the global economic crisis. Biosurfactants (BSs) can carry the prevention, control and management of pandemic out through diverse approaches, such as pharmaceutical, therapeutic, hygienic and environmental. The microbiotas having virulent intrinsic properties towards starting as easily as spreading of diseases (huge morbidity and mortality) could be inhibited via BSs. Such elements could be recognised for their antimicrobial activity, capability to interact with the immune system via micelles formation and in nanoparticulate synthesis. However, they can be used for developing novel and more effective therapeutics, pharmaceuticals, non-toxic formulations, vaccines, and effective cleaning agents. Such approaches can be utilized for product development and implemented for managing and combating the pandemic conditions. This review emphasized on the potentiality of BSs as key components with several ways for protecting against unknown and known pathogens, including COVID-19.

1. Introduction

The pathogens accountable for an atypical respiratory infection emaciated from the Hubei province of Wuhan city, China in late 2019 and discovered as novel coronavirus (from *Corona viridae* family) and there after recognised to be the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), (COVID-19, by WHO) and seems to be homologous with the previous (2002–2003) SARS coronavirus (SARS-CoV) [1,2]. The outbreak was believed to be started from Wuhan seafood market, China via a zoonotic spread and was thus globally communicated up to 200 countries. On March 11, 2020, WHO professed it as pandemic. The coronaviruses usually configured by four different structural proteins, viz., membrane (M), spike (S), nucleocapsid (N) and envelop (E) proteins [1,2]. The host cell invasion along with the viral life cycle of SARS-CoV-2 was depicted in Fig. 1a-c [3,4]. Pandemic results in spreading of infections in too many continents and WHO declares it as a pandemic on its global propagation. It derived the pandemic from two crucial factors: i) the underlying characteristics of microbes and ii) the communication of the microbes with humans. These inherent characteristics of the microbe include novelty, very little or no immunity in the people, explosion about the speed of transmission, common sources, severity and contagiousness of the disease [5]. The COVID-19 is the case that started disseminating across the globe in early 2020; exaggerated many continental economies across the world with an enormous debt, spending and sacrificing human lives in several affected countries. It has electrified the governments around the glove to contravene evolutions on improvement of a green, sustainable and knowledge-based economies and being prepared for imminent outbreaks for an integrated and sustainable bio-based products (United Nations sustainable development goals).

One of the significant bio-based product is the BSs which are revealing feasibility of a smart economy, biodegradability, reliable and sustainable compared to petroleum-based products. The BSs are crucial for managing the pandemic by dealing with the virus and the disease symptoms. Coronavirus (family members) comprised a lipid membrane that encloses its positive sense RNA and vital proteins [6]. The spike

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proteins encapsulated in the lipid membrane helps in maintaining the integrity of the virus and showing a crucial mechanism of infection associated with its transmission via the phospholipid bilayer of the host cell [7]. The BSs (amphiphilic) destroy the virus structure by disrupting their viral membrane by interacting with the viral membrane (via hydrophobic domain).

BSs are classified on the basis of their molecular structures and charges. They are cationic, anionic or neutral in nature. The hydrophobic domains usually contain fatty acids whereas the hydrophilic part comprised of the functional groups like alcohol, organic acid, amino acid or carbohydrate. Based on their chemical structures, BSs can be classified either as high molecular weight (particulate and polymeric BSs) molecules or low molecular weight (e.g. lipopeptides, glycolipids and phospholipids) [8]. Based on the success rate of BSs against the previous outbreaks of corona virus (SARS-CoV and MARS-CoV), they could be considered for their effectiveness against the novel SARS-CoV-2 (similarity in virion structure), hence, could be explored as a new therapeutic (versatile) option towards the management and control of pandemic [7]. However, BSs are now extensively used in a huge number of medical and industrial processes. Their innate versatility made them a brilliant choice for a wide variety of applications related to corona virus [9]. Thus, BSs are nowadays incorporated in developing cleaning agents, hand washes and antiviral facemasks to prevent the spread of the pandemic. The integrated industrial processes for large-scale commercialization requires collaboration in various level/range (funding agencies, policymakers, academia, Stakeholders, clinicians and industry) to kick start innovation for providing a disruptive and transformative solution for fighting against such outbreaks in future [10]. The diversity of different factors (xenobiotics, drug resistance, use of human manipulation or chemicals) created urgency in developing innovative approaches for maintaining environmental management and hygiene and therapeutics. In the future, they can expect more specific applications of BSs by overcoming the challenges associated with large-scale production. The focus of the review article is to exploit pertinent approaches that are helpful in developing BSs based innovative as well as sustainable solutions accomplished with the management of COVID-19 and further preparedness for such outbreaks.

2. The current investigational, diagnostic and therapeutic measures for COVID-19

The real time polymerase chain reaction (RT-PCR) was typically useful for the diagnosis of COVID-19 by using nasal swab. Several investigational techniques include rapid antigen & antibody test, next generation sequencing (NGS), immune enzymatic serological test and droplet digital PCR, chest computed tomographic imaging and chest radiograph findings are usually conducted. Fig. 2d showing different diagnostic testing procedures [11]. Despite of the un-availability of proper medications against COVID-19, some antivirals/antibiotics were repurposed against the pandemic. The drugs being appraised towards COVID-19 management comprised of antibodies (e.g., hyper immune immunoglobulins and convalescent plasma), antivirals (e.g., favipiravir and remdesivir), targeted immunomodulatory therapies (e.g., anakinra, ruxolitinib, tocilizumab and sarilumab), anti-inflammatory agents (e.g., statins and dexamethasone), anticoagulants (e.g., heparin), and anti fibrotics (e.g., tyrosine kinase inhibitors) [12–16] along with numerous supportive care rudiments such as supplementary oxygen and corticosteroids (Fig. 2a and 2b) [11,17]. A total of 31 Covid-19 vaccines (out of

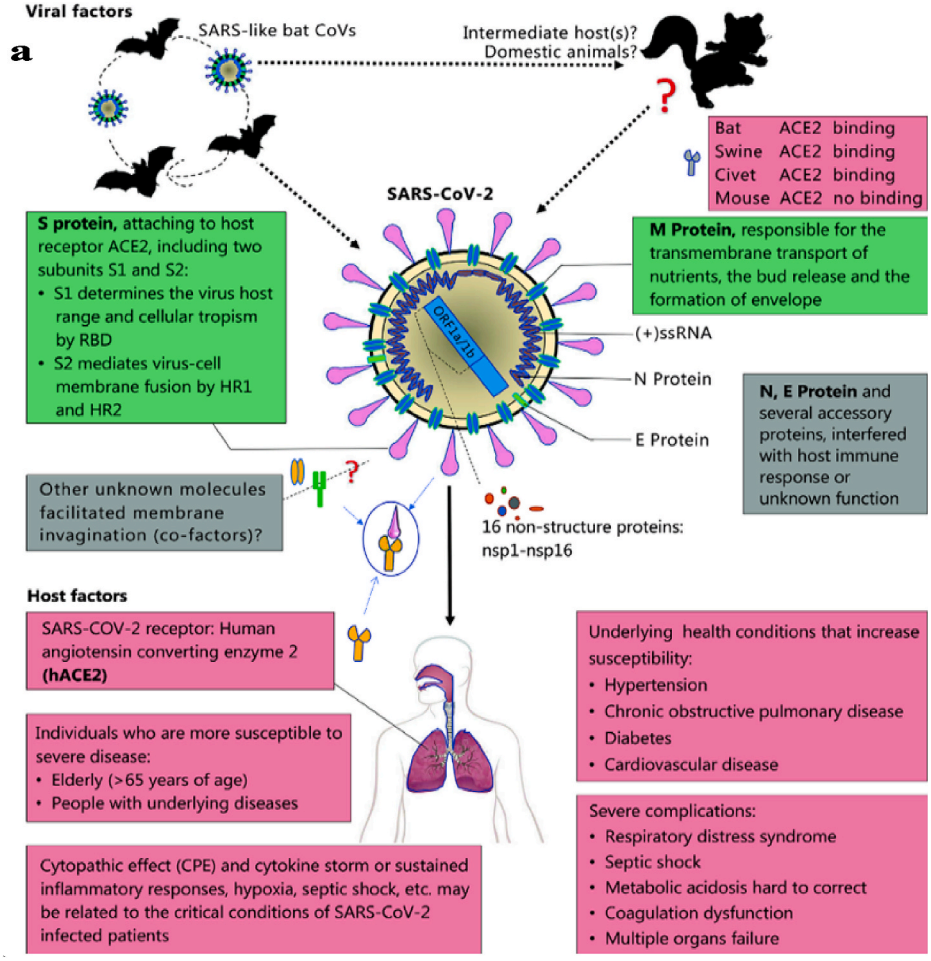

Fig. 1a. Viral and host factors that influence the pathogenesis of SARS-CoV-2. Bats are the reservoir of a wide variety of coronaviruses, including severe acute respiratory syndrome coronavirus (SARS-CoV) -like viruses. SARS-CoV-2 may originate from bats or unknown intermediate hosts and cross the species barrier into humans. Virus-host interactions affect viral entry and replication. Upper panel: Viral factor. SARS-CoV-2 is an enveloped positive single-stranded RNA (ssRNA) coronavirus. Two-thirds of viral RNA, mainly located in the first open reading frame (ORF 1a/b), encodes 16 non-structure proteins (NSPs). The rest part of the virus genome encodes four essential structural proteins, including spike (S) glycoprotein, small envelope (E) protein, matrix (M) protein, and nucleocapsid (N) protein, and also several accessory proteins. S glycoprotein of SARS-CoV-2 binds to host cell receptors, angiotensin-converting enzyme 2 (ACE2), that is a critical step for virus entry. The possible molecules facilitated membrane invagination for SARS-CoV-2 endocytosis are still unclear. Other virus proteins may contribute to pathogenesis. Host factors (Lower panel) can also influence susceptibility to infection and disease progression. The elderly and people with underlying disease are susceptible to SARS-CoV-2 and tend to develop into critical conditions. RBD, receptor-binding domain; HR1, heptad repeats 1; HR2, heptad repeats 2 [3].

344) developed by five different techniques (i.e., viral-vectored, protein subunit, messenger RNA, inactivated whole virus, and plasmid DNA approaches) were in a vast usage after getting conditional/emergency approval under national regulatory authorities/WHO. Most of the protein subunit and inactivated whole-virus vaccines require adjuvants for potentiating immune response [18]. Two new vaccines (receptor-binding domain (RBD)–dimer–based vaccine and plant-based coronavirus--like particle vaccine) were developed by implementing recent technologies (Fig. 2c) [17]. Countries like United States of America (USA), United Kingdom (UK), China, Russia, Canada and India were the leading vaccine manufacturer for COVID-19 [19].

3. Structure and functions of biosurfactants

The BSs developed from numerous microbial species along with few plants are differing from their synthetic counterparts with having an intensive emulsification property at an extensive temperature conditions, stability in extreme pH and salt concentration, biodegradability with significant antimicrobial activity, environment friendly and unveiling a predominantly reduced cytotoxicity. The viral lipid membrane gets intermingled with the hydrophobic domain (comprising of fatty acid or hydrocarbon chains) of BSs resulting in formation of micelles [critical micelle concentration (CMC)] and impacting its emulsification property, thereby disrupting the structure of the virus. The micelles can be targeting the drugs to their target sites by shielding them from the harsh conditions. The BSs are also having utmost biocompatibility, least toxicity and showed less side effects (due to the contents of natural macromolecules like carbohydrates/proteins/phospholipids in their structure) as compared to the synthetic surfactants [8,20].

Besides amphiphilic types, the BSs are classified with their biochemical nature or manufacturing microbial species. These compounds are classified into five main groups with regards to their structure such as a) Glycolipids -rhamnolipids developed from *Pseudomonas aeruginosa* and sophorolipids formed from Candida species. b) Lipopolysaccharides – usually having water solubility and a high molecular weight e.g. emulsan, obtained from the bacteria *Acinotobacter calcoaceticus* c) Lipopeptides-surfactin obtained from *Bacillus subtilis* d) Phospholipids -biosurfactant from *Corynebacterium lepus* e) Fatty acids, hydrophobic proteins and neutral lipids (glycolipids) [21].

The emulsification behaviour of BSs (amphiphilic) is exhibited via reduction of surface tensions across the oil/water interface. They show biological (plants and microbiota) and renewable origins which make them differentiated from their rivalries (synthetic surfactants). BSs exhibit better emulsification tendencies, work across a diversified range of temperatures and proven with a considerably lower cytotoxicity as compared with their synthetic counterparts [22,23]. They can form micellar structures in association with their critical micelle concentration (CMC), which is found to differ within several types of BSs and thus, found to be targeting the virus with a significant impact on their emulsification efficacy and drug delivery. The micelles reveal the potentiality as those of liposomes and could be useful in targeted drug delivery at the site of infection [24]. The versatile BSs along with their wide involvement in food and pharmaceutical industries assured the finding of novel solutions for combating COVID-19 situation, thereby extending a pathway for future research [25–28].

On the basis of stability, structural versatility, biological compatibility, micelle forming ability and low toxicity, BSs are considered to be the propitious biomolecules in the entire pharma industry; useful in designing of therapeutics. The BSs can interact with the cell membrane of organisms, thereby making intracellular targeting. BSs like glycolipids, lipopeptides and Mannosylerythritol developed from Candida species are widely investigated for drug and gene delivery to target cells as well as in immunology; thereby considering them as better options over the synthetic surfactants. BSs can be considered as potential therapeutics in managing the outbreaks/pandemics [8].

4. Mechanism of action associated with biosurfactants in humans

Unlike bacteria, viruses are non-cellular; exist as particles of genetic materials and encased within a protein shell. Such envelope supports the entry of the virus (through fusion) into another new cell and exit through budding. Via endocytosis, the viruses (non-enveloped) get entered into a cell and by cell lysis or exocytosis, released out from the cell. Viruses don't possess any organelle or cell wall essential for their reproduction and thus, for replication solely depends on a host. The BSs revealed utmost biocompatibility with least toxicity compared to their synthetic ancestors [29].

The BSs showed affinity to disrupt the viral membrane of SARS-CoV-2 by interacting with its hydrophobic domain. The BSs having their antimicrobial as well as anti-adhesive properties are based on the membrane damage (because of the leakage of metabolites via modified membrane proteins), metabolites transport, altered generation of energy and alteration in the bacterial lipopolysaccharide system (LPS), thereby plummeting biofilm formation as well as cell adhesion. Several lipopeptides, such as micafungin, echinocandins, daptomycin and anidulafungin have achieved commercial antibiotic status. Moreover, some biosurfactants have shown immunomodulation activities. The activity of macrophage is believed to be reduced by surfactin via down regulation of the expression of several surface molecules of the cell, thus,

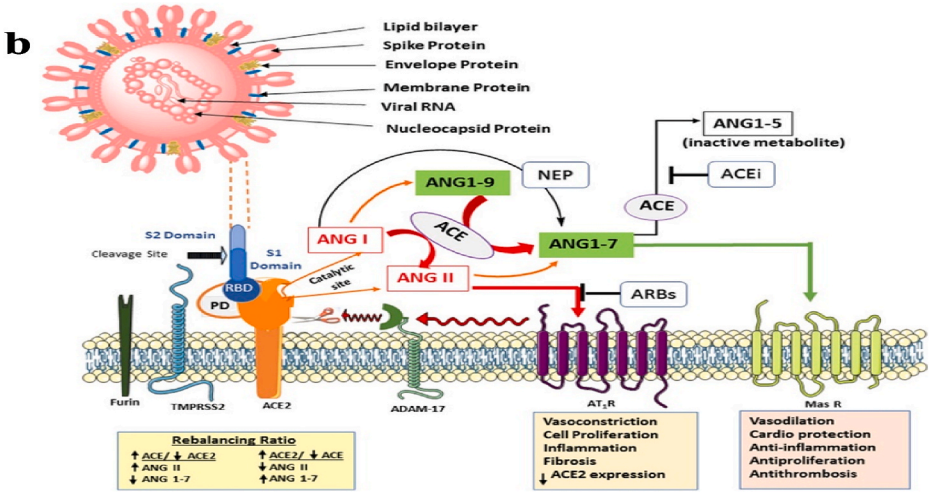

Fig. 1b. SARS-COV-2 virus binding ACE2 and the renin-angiotensin system axis.

considered to be a budding candidate for treating hypersensitivity mediated immune disorders. The anti-inflammatory activity of Surfactin is mediated through inhibition of phospholipase A2, nitric oxide and interleukin. The inhibition of nitric oxide and pro-inflammatory cytokine via Sophorolipid injection (in animals) exhibited treatment for several infections. Despite of the versatility, some BSs developed by opportunistic bacteria must be considered for their in-vivo toxicity and safety [20].

The structure (unique) of BSs urges a compulsion for indulging their functionality (mechanisms of action) and toxicity in the human body towards their medical exploitation. Currently, BSs are widely used as antiadhesive, antimicrobial, immunomodulator and antitumor agents. The contents like glycolipids and Lipopeptides are found to be showing prominent antimicrobial activity and seem to be involved as a resource for new antibiotics discovery. BSs are found to be participating in cellular differentiation, signal transduction, and cellular immune response, used as antitumor agents via interrupting cancer propagation [30–32]. The anti-adhesive and antimicrobial (via membrane damage/disruption) properties of BSs results metabolite leakage through morphological alterations of membrane protein; causing a lack of transport of metabolites and energy generation and deals with alteration of the bacterial lipopolysaccharide system (LPS). This reduces biofilm formation and cell adhesion [31,33]. The lipopeptides have gained the status of antibiotics, such as micafungin, echinocandins, daptomycin and anidulafungin [31]. Surfactin, a potential component that declines the influence of macrophage by varying the expression (down regulating) of quite a few molecules like CD54, present over the cell surface and there by regulate the immune disorders (hypersensitivity) [34]. Surfactin inhibits the response of phospholipase A2 and elicits anti-inflammatory response by regulating the release of nitric oxide and interleukin [35–37]. Similarly, sophorolipid (injection) exhibited inhibition of nitric oxide and pro-inflammatory cytokine; treating different sepsis conditions [38]. Despite of the versatility, some BSs (developed by some opportunistic bacteria) might be considered for their safety and toxicity (in vivo). However, the deficiency in clinical data towards the validation and use of such molecules (in human volunteers and animal models) possess major challenges. Some of the BSs proven themselves, being efficacy in several sectors, fulfilling the requirements of various drug regulatory bodies and possessing themselves as biocompatible and non-toxic molecules.

5. Approaches of biosurfactants in prevention and management of the outbreak

5.1. Therapeutics

Availability of therapy is the most powerful weapon against any kind of outbreak, but, it takes a long period (conduction of clinical trials and the processes of approval) for developing an effective drug/therapeutic against a disease. Targeting a new pathogen either by repurposing of existing drugs or by using already approved molecules (low toxicity) is effective in a stipulated time. In pharmaceutical industry, BSs are seems to be one of the most exciting biomolecules for designing therapeutics for nasal, oral, and dermal applications because of their stability, structural versatility, micelle forming ability, low toxicity, eco-friendly and bio-compatibility [39–43]. The intracellular targeting of BSs is possible because of their ability to interact either with the membranes (surfaces) of the organisms or with the surrounding environment.

5.2. Biosurfactants as anti-viral agents

The production of BSs was found to occur with an experience of depleted resources of the species, along with their natural antimicrobial benefit. The surfactants with their defensive nature were studied; which explored the activation of the envelope viruses via bioactive peptides [44,45]. The dissemination of the influenza virus was inhibited by Cyclosporine A (CsA) (biopeptide developed by the fungus *Tolypocladium inflatum*), intrusive with the viral cycle through inhibition of protein synthesis (budding or assembly) without affecting the adsorption or RNA replication [46,47], enables viral exit from host cells. However, their attachment to the derived membranes (augmented with viral proteins) boost up the tendency of spreading infection [48]. The drug resistance got overcome by targeting the virus life cycle with CsA restricting the spreadability. Lipopeptide linked with low mass antigenic molecules results development of antibodies via stimulation of the immune system. The induction of virus-specific T-lymphocytes (cytotoxic) mediated via synthetic lipopeptide vaccines was effective against influenza [49]. A similar finding has been witnessed against HIV-1 (B and T_h cell response) as well as foot -and-mouth disease (in vivo) [50,51]. Hence, can be considered very exciting towards the discovery and development of new vaccines. Another glycolipid [Sophorolipid (SL)] of microbial origin developed by yeasts has shown potential as an anti-inflammatory immunomodulatory and antiseptic effect in several experimental models (animals) [52]. SL is effective against HIV and herpes virus via acetylation of sophorose head groups, which leads to

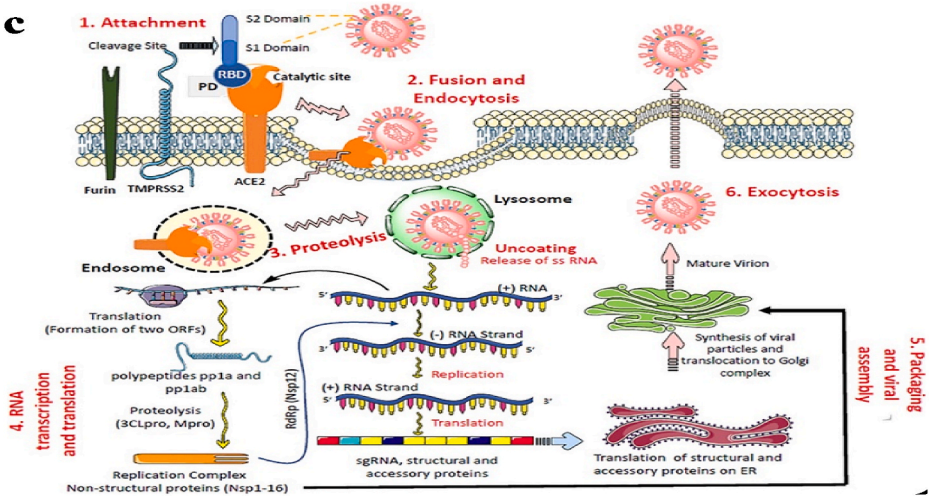

Fig. 1c. SARS-CoV-2 life cycle showing binding, membrane fusion, translation/replication, and virion release. The image was reproduced with permission from Military Med Res (BMC, Springer Nature) & Cellular Signalling (Elsevier) Copyright 2020 [4].

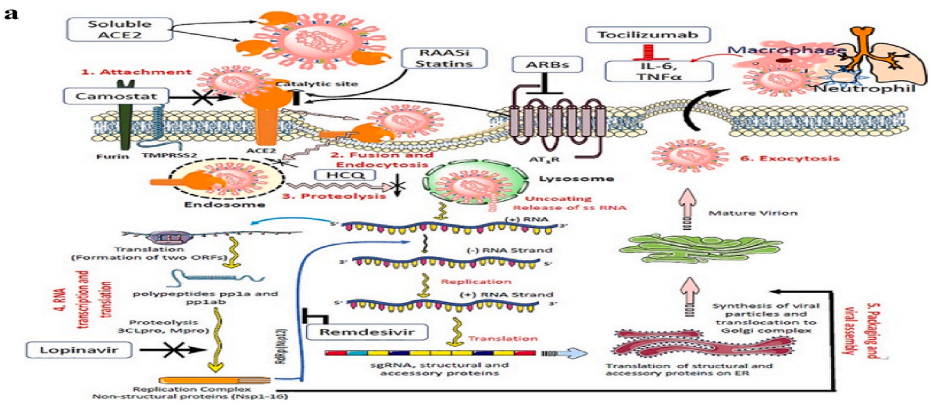

Fig. 2a. Potential pharmacological targets with select repurposed and investigational drugs in the life cycle of SARS-CoV-2.

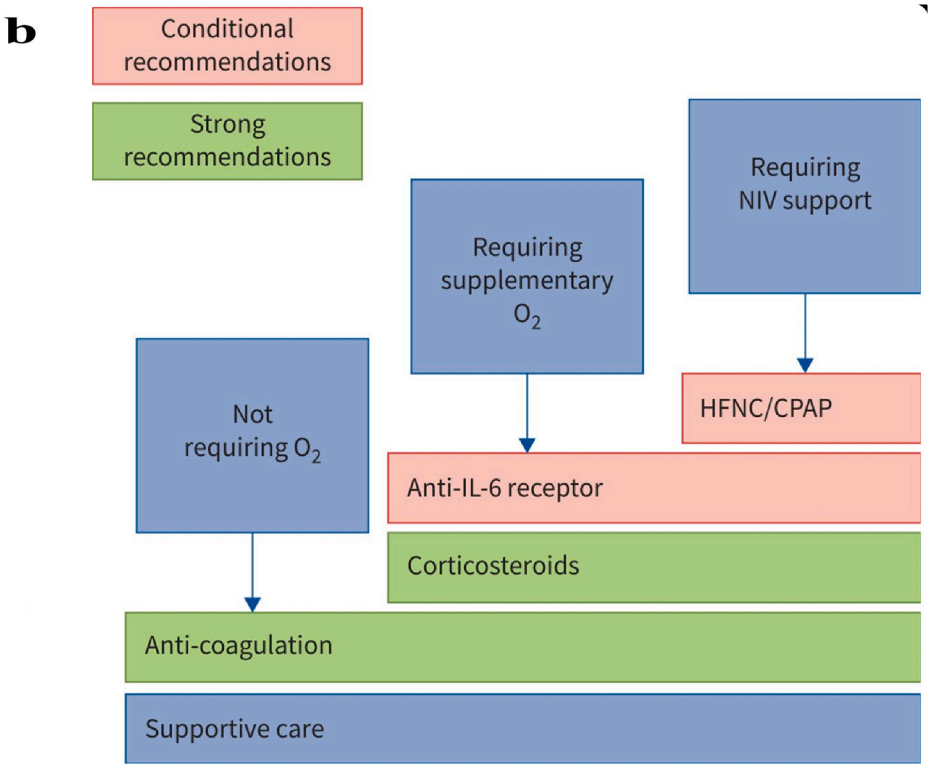

Fig. 2b. Various supportive cares for treatment of COVID-19 patients.

improve its hydrophilicity and thereby promoting cytokine-stimulation and antiviral effects [53,54]. Similar issues have been raised with SARS-CoV-2 [primarily by inhibition of the interaction between virus and ACE2 through solubilisation of virus envelope thereby making degradation of viral components and subsequently by inhibiting the cytokine storm followed by anti-apoptotic genes activation)] [55] which needs an effective screening for identifying budding therapeutics with novel mechanisms for wiping out critical life-threatening effects. Certain enveloped viruses were inactivated by BSs (disturbing the membrane structures of virus through physicochemical reactions, destroying the outer covering [56,57]. The presence of acetyl groups (hydrophobicity with 15 carbon atoms containing one negative charge; along with monomethyl esters) in the structure, BSs promotes anti-viral activity against semliki forest virus [58,59]. It has approved several patents towards antiviral activity of BSs [60–64]. Based on the proven antiviral response, BSs could be a splendid choice against SARS-CoV-2. The BSs (at high concentration) entered the bilayer membrane of viral cell of SARS-CoV-2 and altered their permeability either by formation of ion channel or by membrane disruption, causing a complete disintegration of the capsid protein/viral envelop and resulting viral inactivity. The developed micelles thus behaving as liposomes, and targeting drugs into the desired sites [24]. The anti-viral mechanism of BSs in contrast to SARS-CoV-2 is depicted in Fig. 3 [65].

5.3. *Biosurfactants in Acute Respiratory Distress Syndrome (ARDS)*

Acute respiratory distress syndrome (ARDS) a serious pathogenic syndrome (in COVID-19), deals with an accumulation of fluid in the alveolar region of patient's resulting in systemic insufficiency in oxygen transfer through alveolar membranes and causing multiple organ failure [66,67]. The accumulation of alveolar fluid in connection with SARS-CoV-2 is because of the dysfunctioning of surfactants that leads to a negative consequence towards emulsification and the clearance of liquid from a specific region [68]. BSs seems to be an important area of

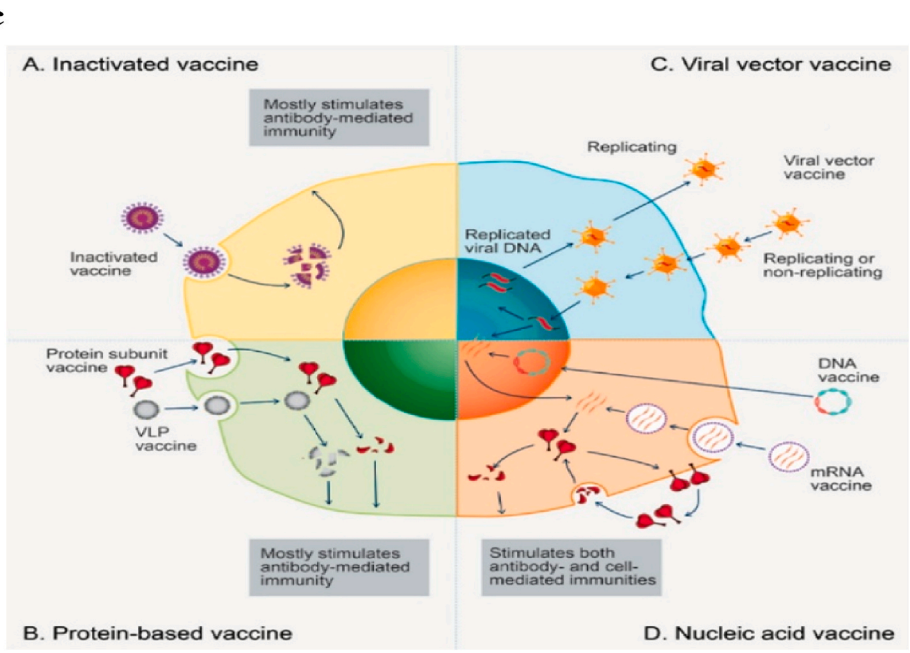

Fig. 2c. Vaccine platforms and their ways of producing immunogen in cells. (A) Inactivated vaccine results in a broader spectrum of antigens when it is taken up and broken down by cells. (B) Protein-based vaccine produces a more focused response to a targeted antigen when it is taken up and processed into multiple epitopes by cells. (C) Viral vector vaccine delivers antigen-encoding DNA to cells and enhances the inflammatory response and immunity. (D) Nucleic acid vaccine enters cells and serves as the transcriptional/translational template for protein antigen synthesis.

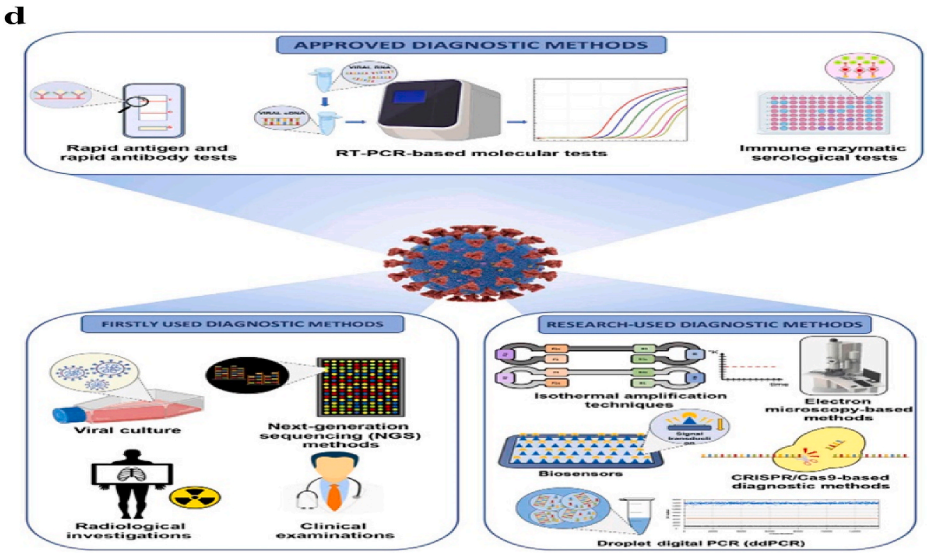

Fig. 2d. Overview of the available clinical, diagnostic and research strategies for the effective diagnosis of COVID-19 infection. The image was reproduced with permission from ACS Cent Sci (American Chemical Society) & Int J Mol Med Copyright 2021 [11,17].

study in connection with discovering novel treatment strategies towards ARDS that could combat the socioeconomic hurdles associated with the usefulness of ventilators (cost, space and training). Thus, it becomes very much essential for making a future study of BSs as a prime therapeutic option towards ARDS (by solubilizing alveolar substrate), which could make positive sense and becomes crucial for managing COVID-19 conditions. It showed a list of clinical trials using surfactant compounds as a therapeutic agent against respiratory diseases in Table 1 [65].

5.4. Biosurfactants and drug delivery mechanisms

As SARS-CoV-2 is predominantly affecting the upper gastrointestinal tract and the respiratory system hence, lozenge or aerosol could be considered as the best mode of drug delivery. The BSs with their micellar nature could be useful in developing stable liposomes for targeting the therapeutics into the infected sites [69]. The self-solubilizing tendency of BSs is playing a prime role in increasing the bioavailability (almost double) and apparent dose proportionality of the drug via an oral route of administration [70]. BSs not only associated with the safety aspect of drug delivery but also showing antiviral impact (natural) at the point of infection (alveoli), in SARS-CoV-2 patients, thereby reducing the virulence and transmission of the disease. However, more research is needed for pondering the clinical efficiency of BSs for being considered as an impactful treatment option. Clinically approved BSs in lozenges or gummies after consumption directly reaches to the parts of mouth and oesophagus, providing symptomatic relief [71]. The vapours developed by BSs could be inhaled through mouth, which reaches to several parts of respiratory tract, providing symptomatic relief.

BSs based micro emulsion (bio-compatible and thermodynamically stable) can be considered as a potential carrier towards increasing the bioavailability, loading capacity and controlled release of the pharmaceuticals. They are useful in encapsulating and/or solubilizing

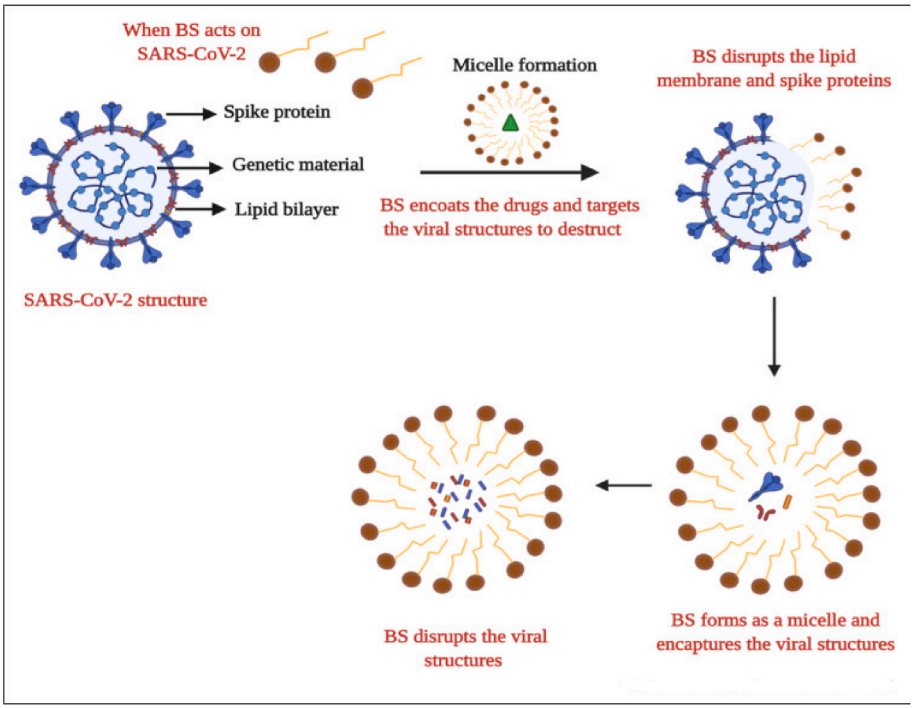

Fig. 3. Possible anti-viral activity of biosurfactants (BSs) on SARS-CoV-2: On SARS-CoV-2 infection, BSs act on viral structures (spike protein and lipid envelope) and ruptures the outer membrane and makes the virus inactive by targeting the genetic material. Once the viral structures are disrupted it forms as a micelle and engulfs the structural parts and breaks down the materials to make it inactive. The image was reproduced with permission from Current Opinion in Environmental Science & Health, Copyright 2020 (Elsevier) [65].

hydrophobic as well as hydrophilic drugs [72]. The BSs such as glycolipids and lipopeptides were used extensively for such purpose and are being potential replacements towards their contemporary synthetic options [73]. The modified micro emulsions loaded with drug molecules were widely used in oral, topical, nasal, intravenous, and ocular routes of administration [72,74]. The recognition of glycolipid sugar chains by carbohydrate-binding proteins made them target specific on cell surfaces [20]. The micelles of BSs (glycolipid) can be expanded into niosomes, liposomes, gels, hexosomes, aerosols and cubosomes for targeted drug delivery. With specific modifications, such agents can be useful in targeting viruses, inhibiting their spreadability in COVID-19 situation too [20,75]. The rhamnolipids can be used as a stabilizer in silver and nickel oxide nanoparticulate drug delivery systems [76–81]. Now it's very clear that the BSs based drug delivery systems are highly potential with their drug delivery efficiency; however, further investigation is required for exploring their impact against virulent microbial species, those having the potential for causing several outbreaks.

5.5. Immunity and vaccines

In normal functioning of immune system, the COVID-19 virus can be removed completely, realizing no symptom in any person. A smart adaptive immune response can be generated via induction/activation of immune cells such as B cells, T cells, neutrophils and macrophages that deals with the development and storage (memory) of antibodies (viral-specific) for subsequent returns of the infection [82]. Another safest mode of activating T cells is by the administration of vaccines. Compared to protein/whole organism vaccines, peptide antigen vaccines are found to be more effective as they are obtained with high purity. They have the limitations of low immunogenicity. Similarly, the bacterial lipopeptides (with varying structure) are found to be the potent, nonpyrogenic and nontoxic adjuvants (immunological) on antigenic coupling for designing vaccines and the activation of the immune system was governed through signalling via toll-like receptor 2 (TLR2) [83]. The cytotoxic T cells (viral-specific) can be induced by lipopeptides (adjuvants) by coupling with viral peptides, i.e. MHC (major histocompatibility complex) against different viral infections. The cytotoxic T cells based immune response can be produced by attaching Tripalmitoyl-S-glycerylcysteinyl-seryl-serine lipopeptide covalently to a synthetic viral peptide [84]. Such preparations are extremely effective in the conditions where a primary immunity against a pathogen is lacking or can be used as a stock for boosting of immunity in amalgamation with additional therapy. However, it's being a serious challenge for boosting immunity with utmost safety and efficacy by using effective formulations along with the adjuvants for vaccine development [85]. Few investigations (reported earlier) revealed the inactivation of viruses (envelopes) by BSs along with the bioactive peptides. The Cyclosporine, a biopeptide developed from the fungus *Tolypocladium inflatum* inhibited the viral cycle of influenza virus by impeding or budding viral assembly after the synthesis of protein [86]. It was believed that targeting viral life cycle can be useful in overcoming antiviral drug resistance, and thereby diminishing the propagation of diseases.

5.6. Inflammation

The immune system of the human body immediately starts fighting against SARS-CoV-2 by recruiting the antigen-presenting cells after its entrance through the ACE2 receptors [87]. As reported, the SARS-CoV-2 positive patients have elevated cytokine level with more viral load, which causes exaggeration of the immune system with damage of healthy cells [88,89]. The cytokine mediated systemic and pulmonary inflammatory retorts (due to elevated IL-2, TNF-α and IL-6) are associated with COVID-19 infections, which leads to increased pulmonary damage causing hypoxia and increased IL-1b and IL-18 level causing organ damage, hypersensitivity and death of healthy cells/tissues, resulting the symptoms of intravascular coagulation (disseminated) and ARDS. However, a moderate T cell response results in low inflammatory response [90–93]. The TLR-2, reactive oxygen species (lysozyme) and cytokines such as IL-6, TNF-α, IL-12, IL-8, IL-1 and Il-18 are demonstrating the antiviral and anti-inflammatory responses of BSs. Hence, BSs could be involved in combating storms of cytokine that help in damaging the lungs, as observed with COVID-19 patients. Thus BSs (glycolipid and lipopeptide) play an important role in defending against the microbial infection and there by induces anti-inflammatory response in the human body [94,95]. The BSs like surfactin, (natural cyclic

Table 1
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	Remifentanil	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	–	Completed	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 Survanta 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
17	Curosurf in Adult Acute Respiratory Distress Syndrome Due to COVID-19	Poractant alfa	COVID-19 ARDS	20	–	Recruiting	France

Respiratory distress syndrome (RDS), Acute respiratory distress syndrome (ARDS).

lipopeptide), showed several biological properties such as anti-cancer, anti-viral, and anti-fungal effects, which gets started via suppression of signalling of survival cells, reduction of cytokine storm and platelet aggregation possessing anti-inflammatory effects [96]. The NF-kB on activation by viral S, N, 7a and 3a proteins enters the nucleus and causes the catalysis of the transcription of procaspase-1and pro-IL-1b. Further cleavage of procaspase 1 and pro-IL-1b into caspase 1and IL-1b were resulted via increased ROS and Ca^{2+}signals and leads to the production of cytokines such as (TNF-α, IL-6, IL-1B, and IL-2) causing necrosis and cell death via cytokine storm. The inhibition of production for heme, develops scarcity of ferrous iron, biliverdin and carbon monoxide, limiting the stress and inflammation mediated by SARS-CoV-2 infection [97–99]. Administration of BSs could help in suppressing the production of NF-kB via stimulation of HO-1 as well as TH1 macrophage cells [100] reducing the production of cytokines (TNFα, IL-1B, IL-6, and IL-2) and suppress their impact in the COVID-19 patients. It was also reported that the emulsification role of BSs (natural components) in vaccines and drugs were found to be successful with non-pyrogenic and non-toxic immunological adjuvants in collaboration with the conventional antigens for treating SARS-CoV-2 disease [101]. Though the hypothesis is yet to be tested for its validation and authenticity, still can be implemented as a mechanism for evolution of novel therapeutics against COVID-19 [102]. Hence, such evidences play a huge role for consideration of BSs as immunosuppressive agents and can be enforced for relieving inflammatory responses (caused by SARS-CoV-2 infection) in combination with other drug(s). The Anti-inflammatory role of BSs against COVID-19 was depicted in Fig. 4 [65].

5.7. Enzymes and biocatalysts

The enzymes encompassing reversed, have extensively used micellar systems in today's emerging era of colloids in biotechnology and

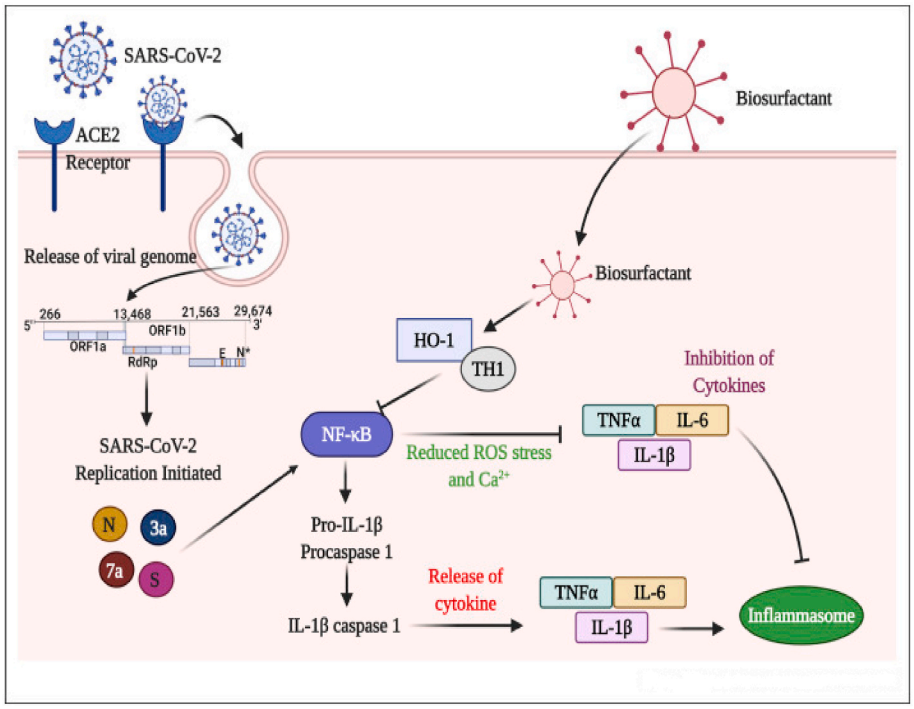

Fig. 4. Anti-inflammatory role of biosurfactants (BSs) against COVID-19**:** The above image depicts the hypothetical role of BSs as anti-inflammatory agents against COVID-19. When the SARS-CoV-2 enters the cell, it binds to the ACE2 receptor following which the TMPRSS2 helps in the cleavage of S protein into S1 and S2 subunits. Subsequently, the viral replication gets initiated resulting into NF-kB 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-kB by triggering the hemeoxidase 1 and TH1 macrophages, which in turn would reduce the effect of cytokine storm and inflammation in the patients affected with COVID-19. The image was reproduced with permission from Current Opinion in Environmental Science & Health, Copyright 2020 (Elsevier) [65].

chemistry. BSs are the amphiphilic moieties which get self-aggregated (with inner polar core and outer part containing hydrocarbons) while used in a limit exceeding their critical micelle concentration (CMC) in presence of organic (nonpolar) solvents. The nanoparticles entrapped under the aggregated structure showed an elevated enzyme activity and leads to be stabilized thermodynamically and can be clearly visualised under the microscope. For example, both in vitro and in vivo impact of DNA cleavage enzymes have been tested, and the results revealed a disruption in vital genes essential for replication of HIV, HSV, Hepatitis B, HTLV and HPV viral infections [103]. An elevated use of CRISPR C_{as} technology in therapeutics signified a diversified impact of gene therapy in targeted/non-targeted drug delivery against several ailments, including COVID-19. These can be implemented for purification and separation of bioactive components, extraction of proteins and enzyme based delivery of drugs [104].

5.8. Drug development

The biomolecules such as lipids offered a wide range of applications in chemistry and in pharmacokinetics of various drug components. The deuterium (hydrogen atom containing both proton and a neutron) is found to be a stable hydrogen isotope and its derivative [Deuterium oxide (D_2O)] is being used extensively in modifying several pharmaceuticals and biomolecules [105]. Similarly, Deuterated BSs developed from the bacteria strain AD7 of *Pseudomonas aeruginosa* containing an erratic levels of carbon substrates and D2O are found to be safer and can be applied in monitoring the status of drug metabolism in biological systems. The BSs can change the drugs and antibiotics, resulting in potentialising their therapeutic efficacy by impeding the progress towards antimicrobial resistance [106]. It can exploit not only pharmacokinetics but also BSs with their antimicrobial assets in development of drugs. BD8 (*Rhodococcus fascians*) isolated from artic soil was lethal against the bacteria (resistant) like *Proteus vulgaris* and *Vibrio harveyi* by making a trehalose lipid BS. The above complex showed a partial inhibition (11–34%) against additional Gram-negative and Gram-positive bacteria and also inhibited (30% at 0.5 mg/mL) *Candida albicans* [107]. The BSs are also found to be reported synergism with antibiotics, sophorolipid in combination with tetracycline inhibited Methicillin-resistant *Staphylococcus aureus* (in vitro). It was also reported that it carried the bacterial inhibition out by maintaining the concentration at a level below to the minimum inhibitory concentration (MIC) [108]. Another emerging treatment protocol was the use of BSs as precision antimicrobials in personalized medicine system [109]. The isolation of 'Bacaucin' a peptide based BSs from *Bacillus subtilis* strain CAU21, revealed its haemolytic effects, cytotoxicity and antimicrobial activity (against Gram-positive bacteria).

Bacaucin-1 (developed via removal of lipid portion along with the opening of ring of the heptapeptide) was effective against *S. aureus* (antibiotic-resistant) strains via disruption of cell membrane, and have revealed (in vivo and in vitro) very less/no bacterial resistance and cytotoxicity towards the mammalian cells [110]. BSs from *Bacillus subtilis* reported antiviral (in vitro) activities against several virus species (envelopes) like retroviruses, herpes and other viruses (non-enveloped) by showing a structural similarity with viruses like MERS, HIV, Hepatitis and SARS. *Bacillus subtilis*-surfactin inactivated (at the concentration 25 μm–80 μm) the viruses by disrupting (through development of ion channels in the viral lipid envelopes and capsids resulting in a depreciation of proteins associated with the process of fusion, penetration and membrane attachment) the viral capsid and lipid membranes [111,112]. Some studies have reported the impact of surfactin analogues and surface-active lipopeptide mixtures as novel potential antivirals against porcine epidemic diarrheal virus and Newcastle disease virus [112–114]. Considering the broad antiviral properties of the above components, they can be suggested for applications against SARS-CoV-2.

5.9. Probiotics

These are the microorganisms (live) providing benefits to the human being as an essential member of gut microbiota, either by maintaining its strength or through its storage. They are contributing towards boosting the immune system. The probiotics (lactic acid bacteria) handle the development of several BSs that are useful as anti-adhesive and antimicrobial agents (against yeast and gram positive/negative pathogens). Bifidobacterium and Lactobacillus are the two major microbiota responsible for expansion of probiotics. Some other members of the group (lactic acid bacteria) are like *Pediococcus, Leuconostoc,*

Enterococcus, Streptococcus, Lactococcus, Sporolactobacillus and some other non-lactic acid bacteria are such as *Bifidobacterium lactis, Propionibacterium, Saccharomyces, Escherichia coli* strain *nissle* and *Bacilluscereus.* They are also effective against multidrug-resistant (MDR) microbiota [115–117] as well as against *Lactobacillus helveticus* [118], lipopeptide obtained from *Bacillus cereus* NK1 [119], *L. paracasei* ssp *paracasei* A20 [120], *Lactobacillus casei* MRTL3 [121] and *Lactobacillus acidophilus* [122,123]. Some evidences have reported that the probiotics might be effective in reducing the risk and the durability of viral infections that will be effective against COVID-19. It was postulated with either through the stimulation of the immune system or via direct viral interaction. However, further investigation is obligatory for determination of viral effects (specific), specifically for RNA viruses and other viruses (respiratory), which may provide a possibility of a stronger and safe option for fighting against the associated infections with emergencies [124]. The mechanistic model of probiotics action against COVID-19 was depicted in Fig. 5 [125].

5.10. Biosurfactants applied for development of cleaning products

During a vital period where it takes time to establish a permanent cure/solution against the pandemic, it can deal the unprecedented situations with cleaning measures (safe and efficient) associated with clothes, homes and surfaces in public areas for combating the viral impact. Anionic surfactant is usually used to prepare for different detergents and cleaning products. The microbes (with their hydrophobic components) bound to the surfactant (via their fatty acid chains) and water (via hydrophilic domain) causing in the microbe's solubilisation (via emulsification). The anionic detergents help in cleaning the surfaces by emulsifying the diets and making them solubilized into smaller droplets [126]. In spite of the incredible antimicrobial efficiency of the bleach (containing sodium hypochlorite), nowadays they are less preferable as compared to the BSs because of their harmfulness (irritation of airways, skin and mucous membranes high risk of injury towards health-care workers, increasing the immunosuppression as well as increased susceptibility towards SARS-CoV-2). The effectiveness of the bleach got reduced because of their decomposition (heat and light) and chemical incompatibility [World Health Organization (WHO), 2014]. BSs are less toxic and eco-friendly as compared to their synthetic variants. The glycolipids (rhamnolipids, mannosylerythritol lipids and sophorolipids) are found to be most effective for cleaning and recognised globally for commercial application. Industries such as Tee Gene, Evonik, BASF and Unilever are commercializing BSs (rhamnolipids and lipopeptide) with their products [10,127–129].

In today's pandemic, the impact of hand sanitizers compared to washing hands by soap and water has put forth a huge debate. The CDC (Centre for Disease Control and Prevention) has revealed that washing hands with soap (lather production) is found to be more effective than using water or hand sanitizer alone [Centres for Disease Control and Prevention (CDC), 2019]. Using alcohol-based hand sanitizers (containing >60% alcohol) are still do not get rid of germs (all types) and might not be efficient against greasy or dirty hands [Centre for Disease

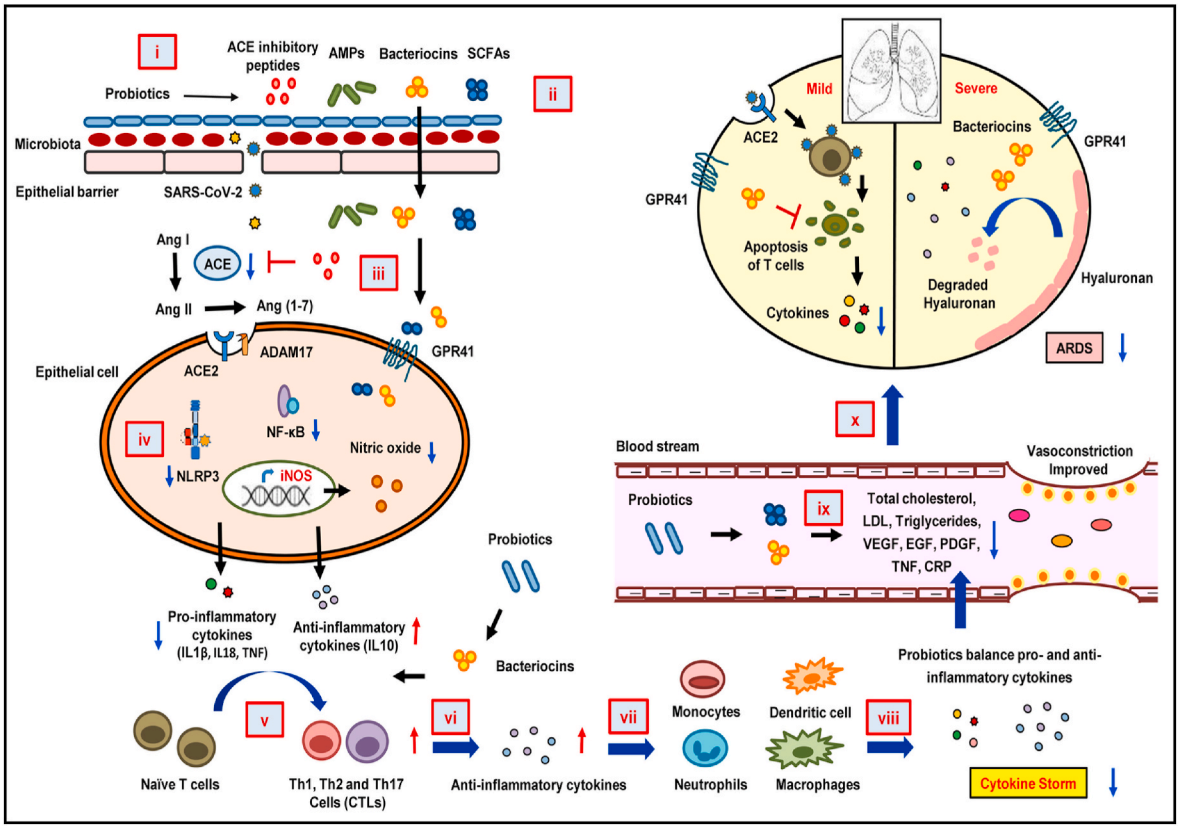

Fig. 5. The mechanistic model of probiotics action against COVID-19. Probiotics induce a stronger epithelial barrier that prevents viral entry through the gut (i) Probiotics modulate gut microbiota and induce the synthesis of SCFAs that regulate blood pressure and inflammation. (ii) Probiotics also release ACE-inhibitory peptides that could reduce angiotensin II (Ang II) expression, thereby inhibiting viral entry into the cell. (iii) Probiotics induce anti-inflammation by supressing NF-κb signalling and reducing the levels of IL 1β, IL 18, NO and TNF. (iv) Bacteriocin as well as proinflammatory cytokines produced by the effects of probiotics modulate Th1, Th2, and Th17 cells. (v) Which in turn help in the production of more anti-inflammatory cytokines. (vi)The anti-inflammatory cytokines regulate monocytes, macrophages, dentritic cells and neutrophils. (vii) To down regulate SARS-CoV-2 infection mediated cytokine storm (viii) resulting in decreased total cholesterol, LDL, triglycerides, VEGF, EGF, PDGF, TNF and CRP level in the blood stream (ix) The reduced cytokine storm and inflammation exerted by probiotics cause the reduction in hyaluronan synthesis, which eventually could improve the ARDS condition in SARS-CoV-2 infection. The image was reproduced with permission from Probiotics and Antimicrobial Proteins. Copyright 2021 (Springer) [125].

Control and Prevention (CDC), 2019]. The repeated and prolonged use of alcohol-based products leads to the develop discoloration and damage to the skin [World Health Organization (WHO), 2014]. The companies like Tee Gene (developed lipopeptide and rhamnolipid BSs based cosmetics) [10,130] and Evonik (preferred sophorolipid BSs for preparing moisturizers, products for refatting, skin conditioners, shampoo, household cleaners, shower gel and hand washes) [131] have developed their commercial products.

5.11. Environmental approaches

5.11.1. Environmental management and control in contrary of potential out breaks

Waste water remains a substantial route of pathogenic transmission leads for developing outbreak or pandemic. BSs with their antimicrobial activities (broad-spectrum), can be applied on waste water for sewage treatment facilities. Thalassogenic infectious diseases are usually developed with respect to the disposal of poorly treated waste water into the sea. The bacteria like *Bacillus amyloliquefaciens* ST34 and *Pseudomonas aeruginosa* ST5 (isolated from waste water) are responsible for development of BSs (surfactin and rhamnolipids) showed broad spectrum antimicrobial activity against drug-resistant *Escherichia coli, Staphylococcus aureus,* and *Candida albicans*. Sewage from quarantine facilities and hospitals (poorly treated) are the leading sources of pathogens. Waste water treatment associated with lipopeptide based lignocellulosic biocomposite; resulting a surge in the adsorption of the biocomposite causes an enhanced sharpness, roughness, stability, and roundness. The entrapment of compounds like heavy metals and xenobiotics, along with the reduction in biochemical oxygen demand (BOD) in the water treatment process, leads to a reduction in pathogenic microbial populations. An amalgamation of bacteria producing BSs of broad-spectrum activity would be recognised as additional therapeutic option in waste water amenities [14,132].

5.11.2. Vector control

The transmission of infectious diseases (either via a biological intermediate (organism) or from person-to-person) is called a vector. The viral ailments like dengue, chikungunya and Zika leads to develop severe outbursts in several provinces globally. Vector-borne diseases like Trypansomiasis (*Trypanosoma lewisi*), and Malaria (*Plasmodium species*) have revealed many threats towards humans life. BSs (lipopeptides)-containing biopesticides showed inferior resistance towards the insects and mosquitos (*Aedes aegypti, Anopheles stephensi, Culex quiniquefasciatuss*) (high potency), along with greater biosafety and selectivity compared to non-target species. The nanoparticles of ZnO (synthesized from *B. licheniformis* EPS) divulged toxicity against viral vectors (malaria and Zika) at a value-added biocompatibility. The pesticides like dichloro diphenyl trichloro ethane (DDT) have concerns such as emergent insect resistance and environmental toxicity. Biosurfactants could be environment friendly and more effective, hence can replace the synthetic pesticides like DDT [15,132].

5.11.3. Personal protective equipments and hygiene

Integrated approaches combined with therapeutics are highly essential for prevention and control of outbreaks. Hygiene and personal protection are the crucial factors need to be concerned for limiting the transmission rate (direct/indirect) of infectious diseases. The discarding of single used masks during the period of pandemic (COVID-19) was a serious concern which has already hampered the biological and environmental safety. BSs based masks (impregnated with layers of silk and BSs) could offer a better protection (antimicrobial, antibiofilm and antiadhesive) against the lethal pathogens. Trehalose lipids inhibit colonization on the surface of silicone and polystyrene when applied on them. BSs from *Lactobacillus jensenii* and *Lactobacillus rhamnosus* are highly effective (possessing antimicrobial, antibiofilm and antiadhesive activity) against multiple drug resistant (MDR) bacteria like *E. coli* and *Acinetobacter baumannii.* The polyvinyl alcohol–BSs mixture are effective against consumables and disinfectants (re-useable) for maintaining hygenicity of hospital equipment. BSs (of high molecular weight) are used as emulsifiers, for developing stable emulsions for cleaning and detergency and showing a better response compared to the synthetic ancestors. BSs (obtained from psychrophiles) could be effective at cold temperatures. Many BSs (sophorolipids and rhamnolipids) based commercial products (for personal and household care) are available in the market by Evonik. BSs as green molecules (next-generation), can be explored for limiting the propagation of pathogens (both unknown and known) during the endemics and pandemics through competent hygiene [16,132].

5.11.4. Control of outbreak through food

It is believed that, the viable pathogens (SARS-CoV-2) contained in frozen foods could be a media for possible transmission of COVID-19. The intensive research outcomes revealed that, COVID-19 virus can survive in numerous surfaces, temperatures (4 to −80 °C for 14–21 days in different frozen food items) and environmental conditions. However, the infectivity and pathogenicity of the virus in those conditions are still unclear. BSs with their potential impact towards packaging in cold environments as well as their role as additives in food industry could make interruption in propagation of infectious disease through food items The BSs as effective detergents along with their antimicrobial property could be useful in surface cleaning of products [14,132].

6. Applications of biosurfactants in diagnostics

6.1. Nanomaterials and nanotechnology

Nanobiosensors (robust, sensitive, cost-effective and simple) can be useful in bridging between routine testing and advanced diagnostics/detection. It is emphasized that the progression of nanoparticles are having less toxic, cleaner and more eco-friendly to combat negative impact on the environmental waste products. Sophorolipid-capped cobalt nanoparticles conjugated with lectins or glycosidases deal with progress of biocompatible particle surfaces used for medicinal and diagnostic applications. The sophorose group's accessibility on the surface of the nanoparticles is one of the important issue towards their biocompatibility [133]. The rhamno lipids based synthesis of silver nanoparticles with BS-161R strain (from *P. aeruginosa*) has proven antimicrobial activity (broad-spectrum) against *Candida albicans* [134]. Nanobiotechnology is being an emerging field growing at a very high pace and now it also becomes necessary to keep their production (BSs-mediated nanoparticles) sustainable and environment friendly. Diagnostics developed based on nanotechnology are highly specific and precise about their efficacy. Thus, the development of diagnostics (with utmost accuracy) is considered to be deserving for the identification of causative agent/organism, followed by building of subsequent response in COVID-19 pandemic.

6.2. Contrasting agents

The BSs mediated synthesis of microbubbles can insist on the synthesis and development of diagnostics (specific, non-invasive and low-cost) for diagnosis of pathogens via molecular imaging. The surface of the bubbles can be conjugated or altered with a disease-specific ligand for the diagnosis of specific diseases. Through ultrasound techniques, the bubbles (kept in the targeted tissue) can be detected by exploiting it (BSs) as a contrast, making the diagnosis more specific and sensitive for detecting the diseases at the early stage of their progression including SARS-CoV-2 [8,135].

7. Remarks on toxicity, biodegradability of biosurfactants in drug delivery approaches

Despite of few negative reports (harmful effects of BSs), BSs have the advanced features to be pain staked for bioremediation, devoid of any detrimental effect to the environment; eco-friendly and safe compared to their synthetic ancestors. The lethality of rhamnolipids reported to be 10% against *Photobacterium phosphoreum*, compared to their synthetic ancestors. Toxicity of sucrose-stearate was found to be homologous with glycolipid, with a faster degradation rate. Marlon A-350 a synthetic analogue revealed high toxicity compared to the BSs synthesized from *P. aeruginosa*. Rhamnolipid developed from *P. aeruginosa* (PG1) was cytotoxic against L292 (cell line) and showed antimicrobial properties thereby applied for bioremediation of crude oil and soil processing. The analytical report of surfactin (from *Bacillus subtilis* HSO121) revealed it as a non-irritant and non-toxic compound, thus found to be safe in detergent preparations [18,132].

8. The regulatory traits associated with the budding biosurfactants

The applicability of surfactants turn out to be more crucial especially in nanoformulations. However, safety of BSs based pharmaceutical products are the most crucial requirement. Regulatory agencies from Europe and USA have customised the guidelines for the assessment of safety and risk–benefit evaluation of BSs. The guidelines of US Food and Drug Administration (USFDA) emphasized on the rationalization behind the applicability of BSs towards development of dosage forms at a reduced concentration. A guideline for industry was published (for conduction of all vital toxicology studies by using Good Laboratory Practice guidelines and ultramodern protocols) for the conduction of safety evaluation (nonclinical) for new excipients by using International Council of Harmonization (ICH) guidelines S2B, S3A, S3B and S7A [136]. BSs can preserve the future of nano therapeutics there by helping in reducing regulatory path length of novel, effective, safe and cost-effective nanovaccines and can fulfil the expectations of regulatory bodies, patients, and industries. It's now become essential for assessing (in vitro and in vivo) the anti-COVID-19 efficacy of microbial biosurfactants. As per regulatory guidelines in pharmaceuticals, BSs should possess safety, pharmacokinetic efficacy, biological and physicochemical compatibility and stability with different components (drug and excipients) to be considered for clinical consideration. Thus, the qualitative BSs must be commended with emerging technologies (cost-effective), with selection of renewable materials followed by innovative techniques for scale-up of bioprocessing as well as characterization [132,136].

Nonetheless of the successful production of BSs (at the laboratory scale) and their potentiality associated with the development of pharmaceutical formulations, the production (scale-up) of BSs is restricted since the final product composition gets exaggerated by several factors. Furthermore, along with the additional bio-based products, the batch-to-batch variability of the structure of BSs could reflect its quality attributes along with the efficacy and safety of the finished product. However, recommending quality by design (QbD) by ICH guidelines (ICH Q8 (R2), ICH Q9, ICH Q10) and risk management through advanced analytical tools such as nuclear magnetic resonance (NMR), chromatographic methods and in-process quality control can leads to adjust the batch to batch variability in scale-up of BSs [15,136].

9. Conclusions and future perspectives

Pandemic preparedness and management are usually carried out for building resilience against the microbes. The nature (environment) is considered to be a foremost transmission vehicle for numerous pathogenic disease outbreaks. Thus, it's now become highly essential to maintain a healthy environment. Exponential disease outbreak via personnel contact can be restricted by implementing sustainable biosurfactants in cleaning and hygiene products. BSs having ample of opportunities to be applied against virulent microbes as well as other pertinent interventions and can also be explored with some advanced technologies like nanobiotechnology and drone applications. Drones could be deployed for spraying of BSs based bio pesticides as well as disinfection of larger surface areas. They can be associated with handling of nanoparticles for laboratory diagnostics; useful in handling of outbreak emergencies. Despite of an incredible and ground-breaking solicitations of BSs in various areas, environment friendly and more often effective compared to the synthetic ancestors, relatively uncompetitive in production; More research needs to be concentrated on the way to reduce the production expense, applicability in unexplored areas, and to discover the effectiveness of specific BSs on unambiguous pathogens for providing better conclusive evidence towards futuristic applications [8]. The SARS-CoV-2 pandemic has imparted a massive impact on public health, resulting an immense hardship towards the public well-being and economy. BSs are recognised as the ideal candidates for this novel situation and targeted for several avenues that found crucial in managing a pandemic of such scale. Exponential spreadability of disease (via indirect and direct contact with people) could be restricted by using BSs in several cleaning and hygiene products. The upcoming technologies (drone and nanobiotechnology) are compatible with BSs. Drones could be implemented in deploying the BSs-based products (disinfection or biopesticide spraying) and also for nanoparticulate based identification in various laboratory diagnostic measures. Although BSs are presenting innovative applications in various areas with having environment friendly approach but, still showing an uncompetitive production rate. They are acknowledged being the valid alternative against ARDS associated SARS-CoV-2 infection. The bio-processing of BSs (with increased production costs) is considered being a significant barrier which could not be overlooked and must be well-thought-out as a pivotal point for futuristic study. The structure and functions of BSs (with incredible versatility) are the essential points considered for a limitless application. Thus, BSs is considered being promising in a situation that is every so often cloaked in misery. With the adequate scientific and research competency, we will not only overwhelm the pandemic issues but also better equip ourselves for future endeavour. It should concentrate on more research to decline the production cost, enhancing applicability in unexplored areas, and explore pathogen specificity of BSs for a superior conclusive evidence.

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