





Sophorolipid: a glycolipid biosurfactant as a potential therapeutic agent against COVID-19

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ABSTRACT

Biosurfactants are natural surfactants produced by a variety of microorganisms. In recent years, biosurfactants have garnered a lot of interest due to their biomedical and pharmaceutical applications. Sophorolipids are glycolipid types of biosurfactants produced by selected nonpathogenic yeasts. In addition to the detergent activity (reduction in surface and interfacial tension), which is commonly utilized by biomedical applications, sophorolipids have shown some unique properties such as, antiviral activity against enveloped viruses, immunomodulation, and anticancer activity. Considering their antiviral activity, the potential of sophorolipids as an antiviral therapy for the treatment of COVID-19 is discussed in this review. Being a surfactant molecule, sophorolipid could solubilize the lipid envelope of SARS-CoV-2 and inactivate it. As an immunomodulator, sophorolipid could attenuate the cytokine storm caused by the SARS-CoV-2 upon infection, and inhibit the progression of COVID-19 in patients. Sophorolipids could also be used as an effective treatment strategy for COVID-19 patients suffering from cancer. However, there is limited research on the use of sophorolipid as a therapeutic agent for the treatment of cancer and viral diseases, and to modulate the immune response. Nevertheless, the multitasking capabilities of sophorolipids make them potential therapeutic candidates for the bench-to-bedside research for the treatment of COVID-19.

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1. COVID-19 and SARS-CoV-2

The world is witnessing the global coronavirus disease 2019 (COVID-19) pandemic that killed more than 4,265,903 people worldwide (>200,000,000 confirmed cases of COVID-19) as of 6 August 2021, and the numbers are still counting [1]. The disease is caused by a novel coronavirus, SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2), which is highly pathogenic, and has the same zoonotic origin as SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) and MERS-CoV (Middle East respiratory syndrome coronavirus) that caused outbreaks in 2002–2003, and 2012 and 2015, respectively [2]. SARS-CoV-2 causes severe respiratory illnesses, such as acute respiratory distress syndrome (ARDS) and pneumonia [3]. In addition, severe cases showed hepatic, gastrointestinal, and neurological complications that could lead to mortality [4]. The transmission of COVID-19 is reported to be human-to-

human through respiratory droplets, direct contact with the infected patients, or touching infected surfaces [5,6]. Airborne transmission of COVID-19, particularly in indoor has also been in debate [7,8].

Though several vaccines are available now in the market, they have their own merits and limitations. To date, there is no proven effective treatment for COVID-19, therefore, prevention measures such as personal hygiene, social distancing, and isolation are the most effective way to minimize the transmission of a virus. Several clinical trials of possible treatments based on anti-viral, vaccines, anti-inflammatory, anticoagulants are in progress [Ahn et al., 2020, 9, 10]. The main treatments being used are drug therapy (use of remdesivir, lopinavir/ritonavir combination, ivermectin, nitazoxanide, and chloroquine/hydroxychloroquine), passive immunization (by transferring ‘convalescent sera’ from a person who recovered from

COVID-19), and respiratory therapy [11–13]. Some of them remain controversial to use for the treatment of COVID-19. For example, WHO doesn't recommend the use of hydroxychloroquine for the treatment of COVID-19, while the use of ivermectin to treat COVID-19 is only advised within clinical trials [14,15]. Antiviral therapies currently used are based on the experience gained during SARS-CoV and MERS-CoV epidemics [9,16,17]. Researchers are also exploring different targets for the potential drugs/vaccines to kill the SARS-CoV2. One of the alternative strategies could be targeting the structural genes for the 'S' protein, or envelope, or membrane protein with small interfering RNAs [4]. The lipid membrane of SARS-CoV-2 has also been suggested as a possible target to kill the virus [18].

Recent perspectives and research studies [19–22] has described the possible role of biosurfactants in COVID-19 management as antiviral, anti-inflammatory, disinfecting agents, cleaning and eco-friendly hand-washing agents. It is hypothesized that biosurfactants, which are microbial-derived surfactants could attack the lipid membrane of the enveloped SARS-CoV-2. In this mini-review, we explain why sophorolipids (SLs) – glycolipid type of biosurfactants, could be a potential therapeutic intervention in managing COVID-19. The hypothetical mechanism of action of SLs in killing the SARS-CoV-2 and inhibiting the progression of COVID-19 is also proposed.

2. Biosurfactants and COVID-19

Biosurfactants are surface-active amphiphilic (having both hydrophilic and lipophilic groups in a single moiety) biomolecules produced by

microorganisms (bacteria, fungi, and yeasts), as extracellular secondary metabolites [22–24]. Structurally, they are highly diverse and can be classified as glycolipids, lipopeptides, phospholipids, lipopolysaccharides, fatty acids, and polymers [23,24]. They find applications in cosmetics, personal care products, and household cleanings, while their potential in pharmaceuticals, environmental clean-up, agriculture, and food industries are also being evaluated by the researchers [24–27]. Being surfactant molecules they can solubilize the membrane, and they have been reported as antiviral agents, particularly for enveloped viruses including coronaviruses [28, Johnson et al., 2019; 20, 29]. Table 1 compiles the biosurfactants reported to have antiviral activities against various enveloped viruses. It can be seen from Table 1, the biosurfactants having antiviral activities belong to glycolipids and lipopeptide classes. The suggested mechanism of antiviral activity of the biosurfactants is the disruption of the viral lipid membrane [Vollenbroich et al., 1997].

Recently, biosurfactants due to their detergent, pharmaceutical, and antiviral activities have been suggested to play a critical role in managing the current COVID-19 pandemic. Moreover, the mechanism of anti-inflammatory properties of biosurfactants including SLs was reviewed by [22]. The authors highlighted the potential role of anti-inflammatory properties of the biosurfactants in managing the COVID-19 pathogenesis. In another study, rhamnolipids (RLs) have been successfully tested as disinfectants against the enveloped viruses, including the bovine coronavirus [20]. The authors also overserved antiviral activity of the RLs-coated surfaces (plastic and fabric) and

Table 1. Biosurfactants having antiviral properties.

Chemical Class	Biosurfactant	Microbial Source	Activity against viruses	References
Glycolipids	Rhamnolipids	<i>Pseudomonas aeruginosa</i> 196; <i>Pseudomonas sp.</i>	Herpesvirus; Tobacco mosaic virus [Crop viral infection]; Bovine coronavirus; SARS-CoV-2	20, 71,72
	Sophorolipids	<i>Candida bombicola</i> [Starmerella <i>bombicola</i>]	Human HIV, Epstein-Barr virus, and Influenza virus	45, 47, 48
Lipopeptide	Surfactin	<i>Bacillus subtilis</i>	Coronavirus (human CoV-229E, MERS-CoV or SARS-CoV); influenza A virus [IAV]; Herpes simplex virus; Simian immunodeficiency virus	Johnson et al., 2019 Vollenbroich et al., 1997
	Fengycin	<i>Bacillus amyloliquefaciens</i>	Cucumber mosaic virus	29
	Surfactin or Fengycin	<i>Bacillus subtilis</i> fmbj	Pseudorabies Virus, Porcine Parvovirus, Newcastle Disease Virus and Infectious Bursal Disease Virus	28

therefore, suggested that the RLs-coated mask and plastic surfaces can be used to stop the spread of the COVID-19 virus. In another study conducted by [30], cotton fabrics coated with lactonic sophorolipids (SLs) along with 1,2,3,4- butanetetracarboxylic acid showed antimicrobial activity against *Staphylococcus aureus*. Because SLs and other biosurfactants have antiviral activities against several enveloped viruses, they should also show similar antiviral activities against coronaviruses. Peptidoglycan-associated surfactin biosurfactant produced from *Bacillus subtilis* has been found as a virucidal agent against enveloped viruses including SARS-CoV (Johnson et al., 2019). These studies suggest that biosurfactants can play potential roles in the management of COVID-19 in multiple ways. However, so far, a specific biosurfactant has not been studied or proposed as a therapeutic agent against SARS-CoV-2 or COVID-19 treatment.

3. Sophorolipids – an introduction

SLs are a group of natural surfactants produced by selected nonpathogenic yeasts (*Starmerella bombicola* a teleomorph of *Candida bombicola*, *C. apicola*, *C. bogoriensis*, etc.) [31–34]. SLs belong to the glycolipids class of biosurfactants, which are low molecular weight extracellular metabolites. Structurally, it is an amphiphilic molecule that consists of a sophorose sugar (hydrophilic group), which is glycosidically linked to a hydroxylated fatty acid chain (hydrophobic). The fatty acid chain has variable carbon atoms with a different degree of saturation, which depends on the microbial strain and hydrophobic carbon source used for its production in the medium [35]. It can be synthesized in the laboratory as a mixture of lactonic and acidic SLs [31,32]. Examples of lactonic and acidic SLs are shown in Figure 1.

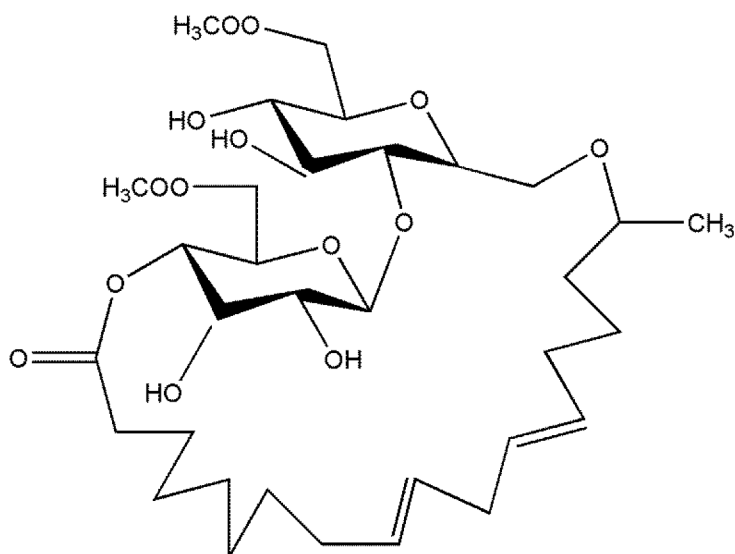
Being surfactant molecules, SLs are highly efficient in reducing the surface and interfacial tensions between two phases. For example, the minimum surface tension achieved by the addition of a mixture of SLs in water is 34.18–28.56 mN/m, and the interfacial tension against *n*-hexane (a non-polar solvent) is 0.99 mN/m [31,32]. The critical micelle concentration of a mixture of SLs produced by *Candida bombicola* using a mixed hydrophilic carbon source (whey and glucose) and oleic acid was found to be 27.17 mg/L [31]. These properties

suggest that SLs are potent surfactants, and can be effective even in low concentrations, which is useful for its therapeutic applications. Apart from excellent surfactant properties, SLs have also shown antimicrobial and antifungal activities [36–42]. It is mentioned as a cosmetic agent in the European Commission's catalog of cosmetic ingredients as cleansing, deodorant, skin protecting and conditioning, antimicrobial, antiseborrheic, humectants, hair conditioning, and antidandruff (European Commission, 2020). It is also available commercially as a cosmetic product such as Sopholiance® S (Givaudan, 2020).

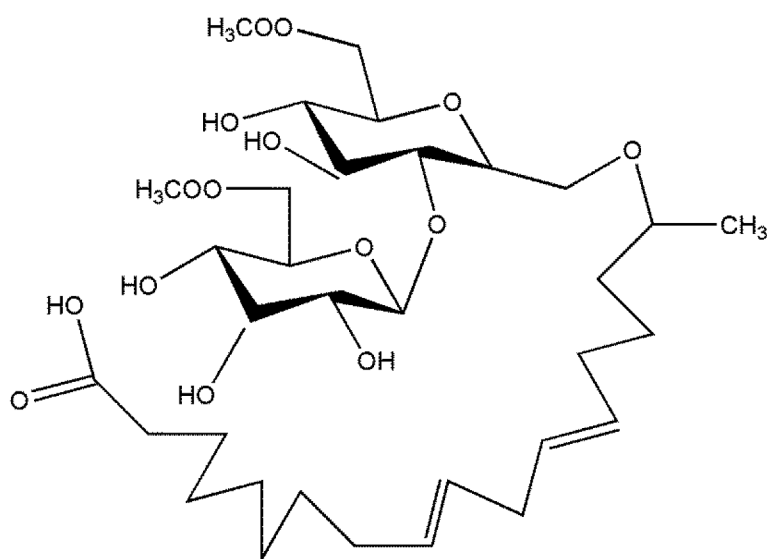
The yeast *S. bombicola* (previously known as *C. bombicola*) is a nonpathogenic yeast and it is not known to cause any disease in humans [43]. The natural habitats of *S. bombicola* are flowers and nectar-feeding insects (bumbees). It is naturally present in honey, fermented vegetable extracts, and grape juice [43.] The yeast *S. bombicola* (previously classified as *Candida stellate*) is also present in wine fermentation and contributes to the sensory character (aroma) of wine [43,44]. Being extracellular metabolites, SLs must also be present in wines, honey, concentrated grape juice, and fermented vegetable extracts. All these facts suggest the possible biocompatibility of SLs for internal use.

4. Properties of SLs that make them potential agents for the treatment of COVID-19 with multiple approaches

The antiviral activities of the SLs and their derivatives have been tested against Herpes virus (Ebstein Barr virus), human immunodeficiency virus (HIV), and influenza virus in *in-vitro* cell-free virus inactivation assay [45–48]. Viral membrane perturbation or disruption has been suggested as the possible mechanism of the virucidal activity of the SLs [48]. The acetyl groups in the structure of SL play a crucial role in promoting its antiviral activity by imparting hydrophilicity to SL [49]. The mixture of SLs has also been reported as an angiogenesis (cancer blood vessel growth) inhibitor in an *ex-vivo* rat aorta ring assay [50], while the lactonic SL (1',4''-Sophorolactone 6',6''-diacetate) has shown a potential anticancer agent *in-vitro* and *in-vivo* model tumor cell lines [33]. Natural



Sophorolipid (Lactonic) C18:2



Sophorolipid (Acidic) C18:2

Figure 1. Structure of lactonic and acidic forms of sophorolipids.

SLs (mixture of acidic and lactonic SLs), as immunomodulators block the lethal effects of septic shocks in male Sprague-Dawley rats in cecal ligation and puncture model by down-regulating the cytokines and significantly improve the survival of animals when administered through intravenous and intraperitoneal injection at a dose of 5 mg/kg rat weight in 4% dimethyl sulfoxide in saline [51].

Following are the listed properties of SLs that are multitasking for the management of COVID-19.

4.1. Lipid solubilization

Surfactants are well known for the solubilization of the lipid membrane of bacteria and viruses. Moreover, the literature suggests that enveloped

viruses are highly sensitive to the surfactants [52], and the lipid contents of the enveloped viruses are easily solubilized by the surfactants [53]. This has also been valid for the enveloped SARS-CoV-2, as WHO has recommended the use of detergents (soaps) to kill the virus on the human body surface [1]. However, the chemical surfactants/detergents are toxic and unsafe for human consumption, as they are derived from petrochemicals. The use of natural compounds such as cyclodextrins and phytosterols has been suggested to target the lipid membrane of SARS-CoV-2 [18]. Therefore, SLs could be an effective virucidal agents to kill the SARS-CoV-2 by disrupting and/or solubilizing its lipid envelope. In addition, since SLs are natural surfactants produced by nonpathogenic yeasts naturally present in wines and various food products, such as honey, we hypothesize that they are potential candidates to be used as a safe and effective preventive treatment for COVID-19.

4.2. Antiviral agent

SARS-CoV-2 is an RNA virus, and it is predicted that it may share functional proteins responsible for the virus replications in humans similar to other human viruses such as HIV. Therefore, antiviral drugs such as Remdesivir effective against other RNA viruses are being tested for SARS-CoV-2. Importantly, SLs has been reported to have antiviral activity against human HIV (RNA virus), Epstein-Barr virus (a Herpes DNA virus), and influenza virus (RNA virus) [45,47,48]. [48], tested different concentrations of SL derivatives against HIV and observed that SL derivatives at 3 mg/ml inactivated virus in a short period (<2 min). The acidic SL (open-ring nonacetylated SL) was found to be more virucidal than a mixture of lactonic SLs. In another *in-vitro* study, the EC₅₀ (50% effective concentration) values of alkyl esters of amino acid conjugated SLs were reported to be <200 µg/ml for HIV [45]. The ethyl ester of leucine conjugated SLs (a mixture of acidic SLs) were found to be the most potent with EC₅₀ value of about 25 µg/ml for HIV. Using the Epstein-Barr virus (EBV) as model organisms on Daudi lymphoid cell lines, the anti-Herpes virus activity of SL derivatives [ethyl ester di acetate SLs, ethyl ester SLs, di-acetate lactonic SLs, acidic SLs and methyl

ester of SLs] was demonstrated by [46]. The ethyl ester derivative of SL (Ethyl 17-L- [(2'-0-b-D-glucopyranosyl-b-D-glucopyranosyl)-oxy]-cis-9-octadecenoate), displayed the best anti-herpes activity with an EC₅₀ value of <0.03 µM. The suggested dosage of tested SLs was between 2 and 30 mg/Kg body weight, via either intraperitoneal, intraarterial, or intravenous administration [46].

Interestingly, all of these viruses (HIV, influenza virus, and Epstein-Barr virus) are enveloped viruses, which further indicate that SLs could be potential antiviral agents against the enveloped SARS-CoV-2. The exact antiviral mechanism of SLs is unknown, though, it is hypothesized that it kills the virus by membrane solubilization [48]. Micelle formation around the virus and its components (genetic materials, spike proteins, etc.) could also play an important role in the antiviral properties of the SLs. The fatty acid chain length, acidic or lactonic form, and the degree of acetylation of SL can affect its antiviral activity. Shorter fatty acid chain lengths, acidic form, and diacetylate ethyl ester SLs are reported to be the most potent antiviral agents [48]. It is expected that different types of SL and its form could also have different virucidal and/or antiviral activity against SARS-CoV-2. Therefore, *in-vitro* or animal model studies for the screening of potent SLs are necessary to find out the most effective SL to kill SARS-CoV-2.

4.3. Immunomodulator

SARS-CoV-2 enters the host through the receptor-binding domain (RBD) present in the 'S' glycoprotein that interacts with ACE2 receptors in the plasma membrane of many cells, including epithelial cells of the oral mucosa [54,55]. The entry of a virus into the host cell induces cytokine storm that causes overproduction of early response pro-inflammatory cytokines like TNFα, IL-6, and IL-1β. This cytokine storm activates coagulation pathways eventually increases the risk of vascular hyperpermeability and multi-organ failure, leading to death [56]. Therefore, drugs which inhibit the immune response (particularly 'cytokine storm' and 'inflammation') to SARS-CoV-2 infection could be useful to stop or reduce the progression

of the disease. Immunomodulatory drugs, for example, baricitinib and melatonin have been suggested recently for the treatment of COVID-19 [57–59]. The purified natural mixtures of SLs have immunomodulatory properties as they have been shown to down-regulate the inflammatory cytokines and up-regulate anti-inflammatory cytokines in Sprague-Dawley rats [51]. They blocks lethal effects of septic shock by significantly reducing the IL-1 β (42.5%, proinflammatory cytokine), TNF- α (50%, proinflammatory cytokine), and macrophage nitric oxide (NO; 28%), and by increasing the TGF- β 1 (anti-inflammatory cytokine; 11.7%) [51]. SLs have been also shown to down-regulate IL-6 in *in-vitro* cellular models using U266 (IgE producing myeloma) cells [60]. The poly(lactonic SLs) decrease (2-fold) MCP-1 (monocyte chemoattractant protein-1) in human mesenchymal stem cells [61]. Due to its immunomodulatory activity, a mixture of SLs was suggested to use for lung injury treatment [62]. Noteworthy, the expression of IL-1 β , MCP-1, IL-4, IL-10, and IFN- γ is reported to be increased in COVID-19 patients. This suggests that SLs could attenuate the ‘cytokine storm’ caused by SARS-CoV-2.

4.4. Anticancer activity

Cancer patients have a higher risk of severe illness from COVID-19 due to their immunocompromised system. Among all cancers, patients with blood cancer have a ten-fold higher risk, and patients with metastatic cancer have about a six-fold higher risk of severe events and death [63]. SLs and their derivatives have been shown to be effective/lethal against cancer cells. For example, purified lactonic sophorolipid (1',4''-sophorolactone 6',6''-diacetate) effectively kills human liver cancer cells [36]. 64, reported the cytotoxicity of natural mixture of SLs and its various derivatives such as, ethyl ester, methyl ester, ethyl ester monoacetate, ethyl ester diacetate, acidic SL, and lactonic SL (1',4''-sophorolactone 6',6''-diacetate) against human pancreatic cancer cells [64].

65, studied the cytotoxicity of 10 purified SL molecules on human esophageal cancer cells. The authors reported that the cytotoxic effect varies with degree of saturation of fatty acid, acetylation of sophorose and lactonization or ring opening in

SL. The authors concluded that the diacetylated lactonic SL with one double bond in fatty acid chain showed strongest cytotoxicity, while acidic SL showed poorest cytotoxicity against human esophageal cancer cells. The SLs and its derivatives also found effective against human cervical cancer cells [66,67]. Recently, 33, tested the antitumor activity of SL (1',4''-Sophorolactone 6',6''-diacetate) loaded polymeric nanocapsules using CT26 murine colon carcinoma (*in-vitro*), and female Balb/c mice (*in vivo*). After 3 days 80% inhibition in the viability of the tested cancer cells (CT26 colon cancer cells) was observed by the authors. The toxicity effect on the normal cell lines was non-significant (CCD-841-CoN normal colon epithelial cells). About 60% inhibition on the tumor growth was observed in *in-vitro* study using the encapsulated SL formulation (20–60 μ M SL) [33]. The SL nanocapsules (200 μ L with SL at a dose of 10 mg/kg) administered to mice, via intravenous injection inhibited the tumor growth (about 29%) and weight, without affecting the subject, which suggests that SL nanocapsules could be effectively and safely used for the treatment of colon cancer [33]. The anticancer effect of SL is due to the “depolymerization of the mitochondrial membrane and enhanced intracellular calcium levels [67]. Since anticancer effects of SL could be obtained without compromising the immune system, the SL could be a blessing for patients suffering from cancer and COVID-19. However, that needs to be tested systematically in *in-vitro* and *in-vivo* in animal systems.

5. The Possible mechanism of action of SL

Like other coronaviruses, SARS-CoV-2 is a spherical or pleomorphic enveloped, positive-sense single-stranded RNA virus. The genome of coronaviruses (CoVs) encodes four major structural proteins, spike (S), envelope (E), membrane (M), and nucleocapsid (N), and several nonstructural 5 to 8 accessory proteins (Figure 2a). Among them, spike (S) glycoprotein plays an essential role in viral attachment to the ACE2 (angiotensin-Converting enzyme 2) on host cells (like a human respiratory epithelial cell) [18]. This attachment is essential for the pathogenesis of a virus. The two possible mechanisms of SL are:

the solubilization of virus envelope, thus degrading the components of the virus, and inhibiting the interaction of virus and ACE2 (Figure 2b); and the inhibition of the cytokine storm and activation of anti-apoptotic genes (Figure 3). Of note, SARS-CoV-2 mutations *in-vivo* after infection may lead to the generation of several intra-host variants of the virus, one of the reasons for heterogeneous development of signs and symptoms and an unpredictable clinical outcome in infected individuals [68]. Therefore, disruption of the virus envelop could be the potential strategy to inhibit the pathogenesis of SARS-CoV-2. In addition, the administration of SL could be effective in inhibiting cytokine storms that may reduce the adverse outcome of COVID-19.

6. Issues and challenges associated with SLs

SLs are produced as a mixture of acidic and lactonic forms with variable lipophilic chain lengths. Due to their surfactant activity, acidic lactonic or a mixture of SLs can certainly solubilize the lipid

protective outer shell of SARS-CoV-2. However, the immunomodulatory and anticancer properties of the SLs are reported in limited studies, which still need to be further verified. Particularly, the type of SLs [either acidic, lactonic, acetylated, deacetylated, or mixture] responsible for such immunomodulation and/or anticancer activities need to be verified. The crude mixture of SLs has shown varying levels of antiproliferation and anticancer activities in literature as highlighted by 69. A study reported that the purified lactonic SL [96%, C18:1] had reduced the viability of colorectal cancer, as well as normal human colonic and lung cell lines *in-vitro*, in a dose-dependent manner, while it increased the tumor burden in mice [69]. In an *in-vivo* study, the purified acidic SL (94%) decreased the cell viability of colorectal cell lines without negatively affecting the colonic epithelial and lung cell lines and highlighted the advantage of acidic SL over lactonic SL for anti-cancer activity [69]. However, *in-vivo* effects of acidic SL are not studied yet. Overall, there is not a single clinical study on the use of SLs as a therapeutic agent

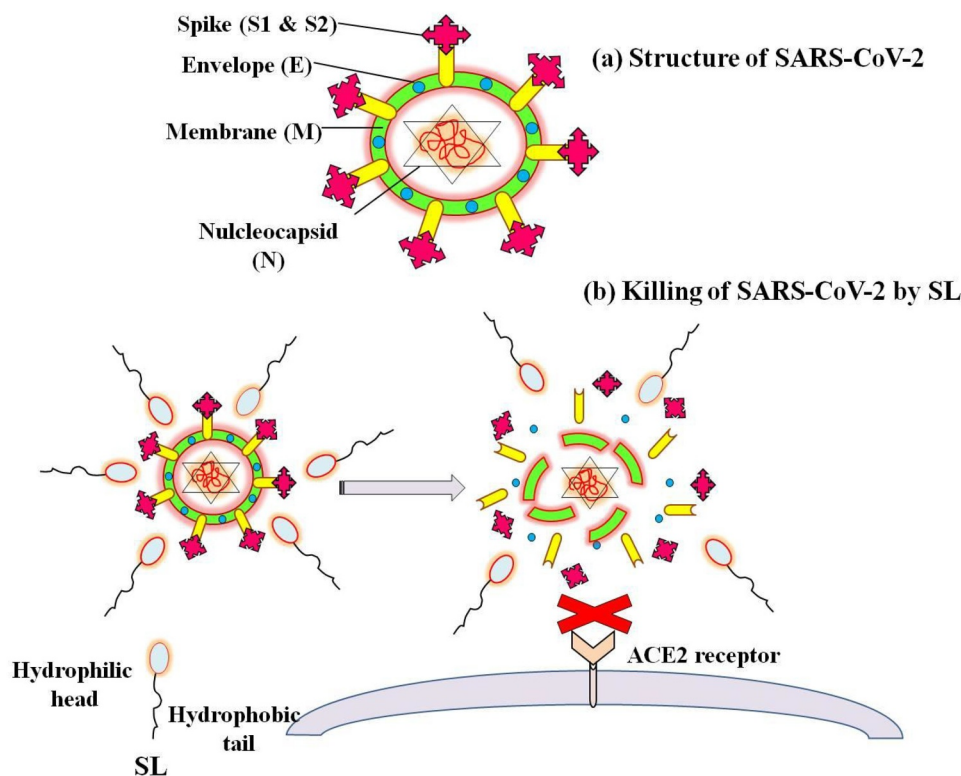


Figure 2. Structure of SARS-CoV-2 (a), and proposed mechanism of killing SARS-CoV-2 by sophorolipids (b).

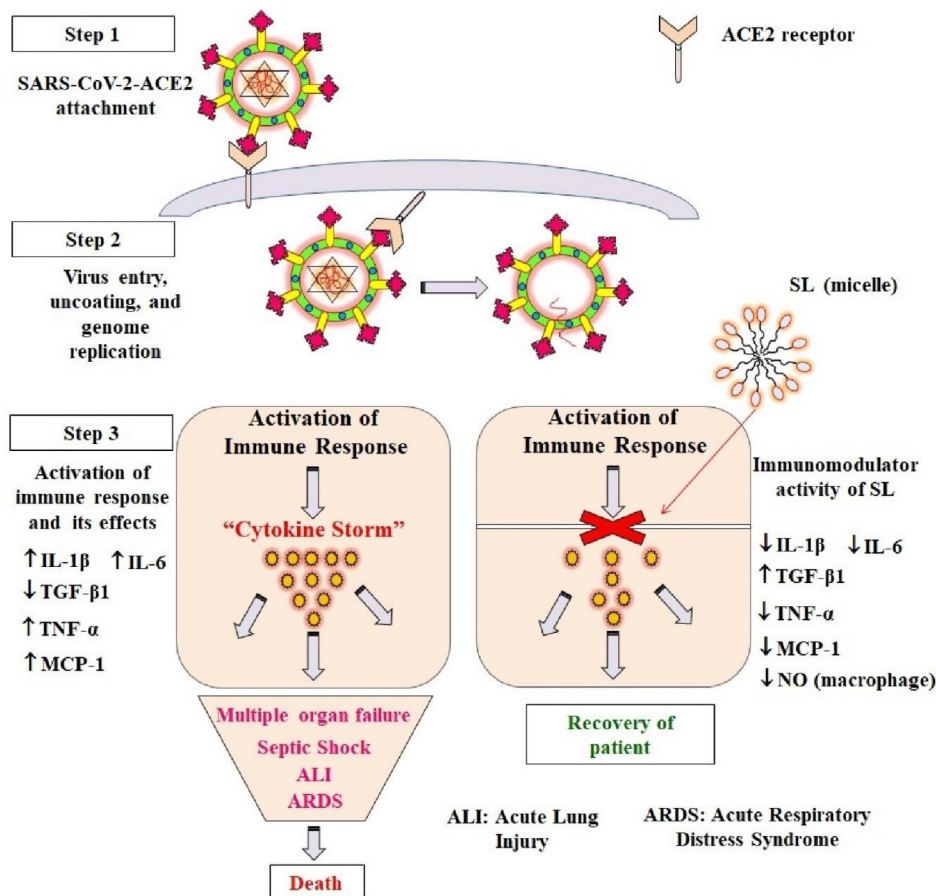


Figure 3. Possible mechanism of action of sophorolipids in inhibiting the progression of COVID-19 by attenuating the 'cytokine storm' caused by SARS-CoV-2.

covering its effectiveness, side effects, and toxicity on patients. Therefore, these issues of SLs have to be addressed well before their use in any clinical studies of COVID-19 treatment.

7. Concluding remarks and future scope

SL is a natural surfactant that is safe for human use and is already in the market for cosmetic applications. This makes SL a perfect therapeutic candidate for the bench-to-bedside research for the treatment of COVID-19. Besides surfactant, its antiviral and immunomodulatory properties have also been established in various models (*in-vitro* cellular models and *in-vivo* animal models). It has been administered via topical (in cosmetic products to humans), intravenous and intraperitoneal injection to animal models without showing toxicity to the tested model. So far, the major research has been focused on identifying anti-viral mole-

cules that target the spike protein as it mediates viral entry and induces host immune responses. However, not all patients experience the same level of immune response, which could be attributed to the mutation that occurred in the genome of SARS-CoV-2. Furthermore, the presence of these biologically heterogeneous haplotypes of the virus and their variable interaction with individual genetic and epigenetic characteristics makes it difficult to predict the course of disease in a single individual. Which makes it challenging to develop universal treatment for all COVID-19 patients [70]. Therefore, a treatment like using SL-therapeutic intervention that targets SARS-CoV-2 in multiple ways could provide a better clinical outcome for COVID-19 patients than just antiviral agents alone. The Sustainable Development Goal (SDG 3: Good Health and Well-being) could also be achieved by the SL-based treatment of COVID-19.

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