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REVIEW ARTICLE

The Potentials of Biosurfactants as Anti-Inflammatory and Anti-Viral Agents Against Covid-19: A Mini Review

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ABSTRACT

Infection due to strain of severe acute respiratory syndrome coronavirus 2 (SARS COV2) has grown to be of global public health significance. Biotechnology uses living organisms such as microbes to produce metabolites like biosurfactants. Biosurfactants are ampiphilic surface active biomolecules that were proven to have therapeutic function against some groups of microbes including viruses. They also have anti-inflammatory potential through their interaction with viral membranes and macromolecules to decrease cytosolic phospholipase A2, which is the beginning of an anti-inflammatory response, and are recognized structurally by toll-like receptors (TLR-2), which are released when neutrophils are stimulated. They can also play vital role in aiding the human body to have inflammatory response. The functional groups of biosurfactants interact with the viruses membrane structure. Some groups of biosurfactants cause physiochemical processes that render viruses inactive. Therefore it can generally be understood that biosurfactants destroy the virus's envelope and the viral membrane's structures. The principle behind biosurfactant's anti viral property is due to the hydrophilic properties that are within the acetyl groups. Additionally, the hydrophobic properties of biosurfactant are also important in making it to have antiviral activity. These activities of biosurfactants against viruses make it to be potential anti-inflammatory and anti-viral agents against Covid-19. Therefore this paper is aimed to produce a mini review on the anti-inflammatory and anti-viral potential against Covid-19. And the review also highlights some of the desirable properties and benefits of biosurfactants as anti-corona viruses.

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INTRODUCTION

The surface and interfacial tension between different media are reduced by surfactants, which are surface-active compounds with dual characteristics having both water-loving and water-hating functional groups. Theseagents are classified into chemical and biological surfactants based on their origin (Santos *et al.*, 2017). They are also classified into glycolipids, phospholipids, lipopeptides, as well as higher molecular weight or polymeric surfactants based on monomers they are composed of (Fardami *et al.*, 2022). Biosurfactants are secondary metabolites produced by a variety of microorganisms, including bacteria, molds and yeasts. They are categorized according to their structural components and theprocducing microbes such as *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Lactobacillus* sp., *Candida bombicola*, *Torulopsis bombicola*, *Penicillium chrysogenum* and *Aspergillus versicolor* (Perfumo *et al.*, 2017: Fardami*et al.*, 2022). During growth, they are either produced within the cells or excreted in medium (Santos *et al.*, 2016).

Biosurfactants are a diverse group of surface-active compounds produced by microorganisms (Inès *et al.*, 2023). These compounds have the ability to reduce surface tension and increase the solubility of hydrophobic compounds in aqueous solutions (Patel *et al.*, 2023). Biosurfactants have a wide range of applications, including in the oil and gas industry, environmental remediation, and bioremediation (Singh, 2023). Recently, there has been growing interest in the use of biosurfactants as antiviral agents, particularly in the context of inhibiting viral infection (Kisla *et al.*, 2023).

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Viral infections remain a significant health concern worldwide, and traditional antiviral therapies can have limitations such as toxicity, resistance, and high cost (Sokhela *et al*., 2023). Biosurfactants offer a potential alternative approach to inhibiting viral infections (Ukaegbu *et al*., 2023). Studies have shown that certain biosurfactants can disrupt the lipid envelope of enveloped viruses, leading to viral inactivation or inhibition of viral replication. The lipid envelope is a critical component of many viruses, and disruption of the envelope can prevent the virus from entering host cells or replicating (Tripathy *et al*., 2023).

Biosurfactants have been shown to be effective against a range of viruses, including human immunodeficiency virus (HIV), herpes simplex virus (HSV), influenza virus, and respiratory syncytial virus (RSV) (El Khalloufi and Oudra, 2023; Sil *et al*., 2023; Antony *et al*., 2022). For example, rhamnolipids, a type of biosurfactant produced by Pseudomonas aeruginosa, have been shown to inhibit the entry and replication of HIV in human cells (Vanreppelen *et al*. 2023). Similarly, sophorolipids, another type of biosurfactant produced by yeast, have been shown to inhibit the entry and replication of HSV in human cells (Karnwal *et al*., 2023).

In December 2019, a new strain of coronavirus that causes the coronavirus illness 2019 (COVID-19) developed and spread globally. A global public health emergency has emerged because of the COVID-19 in different countries of the world (Venugopal *et al*., 2020). Apart from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-1) the brand-new strain of the coronavirus with rapid human-to-human transmission, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a global public health disaster and claimed many lives (Chen *et al*., 2019; Chan *et al*., 2020). After contracting the infection, the infected individuals primarily depend on their immunity to fight the virus, with supportive therapy being recommended if difficulties arise (Grasselli *et al*., 2020). According to research, the expression of angiotensin-converting enzyme 2 (ACE2) in host cells is the initial stage in disease initiation process of the new coronavirus strain (Hoffmann *et al*., 2020).
The defense system sends a lot of cells to kill the virus once it gets inside the lungs (Huang *et al*., 2020). The system becomes overactive once the cytokine storm(an immune reaction in which many cytokines are released into the blood too quickly) forms and kills the healthy cells (Mahalaxmi *et al*., 2020). In addition to the virus' ability to defy therapy, the immune system presents a significant challenge when choosing the best course of action and vaccine. The immune system's ability to maintain balance is weakened by SARS-CoV-2, which also causes the cytokine storm. The cytokine storm has been associated with the considerable challenges seen in COVID-19 patients. After attaching, the spike protein splits in two, causing a conformational shift that makes it easier for the virus to fuse and enter the cell. The stages of viral replication in cells were recently thoroughly described by Naughton *et al*. (2019). Over the past ten years, the number of BSs with a medical focus has increased. Biosurfactant fights a variety of diseases because of its antiviral, antibacterial, and antifungal properties (Naughton *et al*., 2019). The use of biosurfactants as antiviral agents is still in the early stages of development, and more research is needed to fully understand their potential applications. This mini review is aimed to highlight the potential application of biosurfactants as anti viral and anti inflammatory agents.

ANTI-INFLAMMATORY POTENTIAL OF BIOSURFACTANTS

Phospholipase A2 (PLA2) facilitates the secretion of arachidonic acid (AA). Different PLA2 variants are collectively referred to as cytosolic phospholipase-A2 (cPLA2). An inflammatory response occurs as arachidonic acid is released and changed into inflammatory mediators. Eicosanoids, which are generated as a result of arachidonic acid, are first created in order to maintain the inflammatory process. Biosurfactants interact with cell membranes and macromolecules to decrease cytosolic phospholipase A2, which is the beginning of an anti-inflammatory response, and are recognized structurally by toll-like receptors (TLR-2), which happened when neutrophils in an in vitro model were stimulated by *Rhodococcus ruber*'s trehalolipids to release inflammatory cytokines (Baeva *et al*., 2014). The lipids were being supplied by these neutrophils. According to Chereshnev *et al*. (2010) and Gein *et al*. (2011), induced R. ruber glycolipids in mononuclear cells facilitate the synthesis of IL-12, IL-18, and reactive oxygen species (ROS) and increase the production of TNF-a, IL-1b, and IL-6. In rat and fish models, surfactin administration decreased levels of pro-inflammatory cytokines while raising levels of anti-inflammatory cytokines (Ramasami *et al*., 2009; Giri *et al*., 2016). According to research by Zhang *et al*. (2015), the antibacterial lipopeptide biosurfactant surfactin was found to inhibit lipopolysaccharide-induced signaling pathways, impair macrophage function, prevent IL-12 expression, and reduce the expression of the toll-like receptor-4 protein, which increased the anti-inflammatory effect.

According Park *et al*. (2013), *Staphylococcus aureus*'s surfactin was abled to considerably decrease the proinflammatory mediators which also raised STAT-3phosphorylation, preventing the synthesis and release of haeme oxygenase-1 and blocked the lipoteichoic acid-induced signaling pathway (HO-1). The impact of biosurfactants produced by yeast species with anti-inflammatory activity was also indicated by a few small investigations that were carried out. Immunoglobulin E (IgE) levels, IL-6, STAT3, and TLR-2 mRNA expression, as well as lung inflammation, were all reduced by sophorolipids (SLs) from *Candida bombicola* (Hagler *et al*., 2007; Vakil *et al*., 2013). Therefore, the study showed that sophorolipids downregulate the IgE coding genes, acting as an anti-inflammatory molecule and possible therapeutic substance (Hagler *et al*., 2007; Bluth *et al*., 2006).

In an in-vivo experiment, sophorolipidswere found to have anti-inflammatory properties and reduced sepsis-related mortality in a rat model (Hardin *et al*., 2007; Mueller *et al*., 2006). Similar to this, SLs reduced nitric oxide (a reactive oxygen species), regulated inflammatory responses, and enhanced survival rates in a different rat model research (Bluth *et al*., 2006). It has been shown that both natural and synthesized sophorolipids have strong anti-inflammatory, spermicidal, and anti-HIV activity (Shah *et al*., 2005). The SLs inhibit the expression of inflammatory cytokines (Mueller *et al*., 2006), and these results suggest that SLs would be a promising therapeutic agents for immunomodulation or anti-inflammatory in disorders that are chronically inflammatory. *Pseudomonas antarctica* secretes mannosylerythritol lipids, which have anti-inflammatory effects since they have suppressed the inflammatory mediators (Morita *et al*., 2011).

MECHANISM OF TISSUE DAMAGE AND INFLAMMATORY RESPONSE OF THE BODY AGAINST COVID 19

The body's defense system promptly mobilizes a huge quantities of cells to fight the virus, especially by securing the help of lymphocytes, after the virus has entered the vertebrate host cell via (Yang, 2020). High levels of cytokine storm have been found to be present in COVID-19-positive individuals, and these levels are also related to the viral load in these patients (Wang *et al*., 2020). When a cytokine storm develops, the immune system becomes overactive and kills healthy cells (Mahalaxmi *et al*., 2020). Furthermore, larger lymphocyte and IL-6 levels unintentionally cause more pulmonary injury (Akhmerov and Marban, 2020). Furthermore, while contemplating the best course of therapy and vaccination possibilities, the virus's capacity to elude the immune system poses serious challenges. The resultant harm may be brought on by direct SARS-CoV-2 infection of cells, hypoxia brought on by pulmonary injury brought on by immunological reactions (Harshada, 2014).

In the course of the cytokine storm, excessive levels of cytokines like IL-1b and IL-18 are created, which may permanently harm different organs. The biosurfactants are well known for their significant contribution to the body's defense against disease causing microorganisms and their ability to reduce inflammation (Sajid *et al*., 2020). Different anti-microbial disorders have been successfully treated with the help of the glycolipid and lipopeptide types of biosurfactants (Liu and Li, 2020). One of its subtypes, surfactin, a naturally occurring cyclic lipopeptide, has been demonstrated to possess a variety of microbial activities (Singh and Cameotra, 2004). These activities are started by blocking the signaling of cell survival, platelet aggregation, and lowering the cytokine storm by putting forth anti-inflammatory effects.

In order to reduce the effects of the cytokine storm brought on by viral infection in the infected individuals, it may be possible to employ surfactants of biological origin. Speculative mode of action for biological surfactanat's ability to reduce inflammation in the COVID-19 illness has been speculated. The Spike of SARS-CoV-2 is split in two upon contact, which causes a conformational shift that facilitates the attachment of the virus and its penetration into the cell. Viral proteins N, S, 3a, and 7a stimulate nuclear factor Kappa beta pathway, a common pathway involved in numerous diseases. Pro-IL-1b and procaspase-1 are both transcriptionally regulated by NF-kB, which, upon activation, moves into the nucleus. Pro-IL-1b and procaspase 1 are split into IL-1b and caspase when other signals, such as elevated Ca2+ and reactive oxygen species, are recognized. This triggers the release of many mediators, which culminates in a cytokine storm causing cell destruction and death. Since heme is necessary for the creation of biliverdin, ferrous iron, and carbon monoxide, which might reduce inflammation and stress brought on by SARS-CoV-2 viral infection, it has been discovered that COVID-19 patients have heme production that is inhibited (Fujioka *et al*., 2017; Takeda *et al*., 2017; Saimmai *et al*., 2020). By activating the HO-1 and TH1 macrophage cells, the biological surfactant may reduce the production of NF-kB if given to COVID-19 patients (Rodrigues *et al*., 2006).

This would therefore lessen the production of cytokines including TNFa, IL-1B, IL-6, and IL-2, which would lessen the impact of the cytokine storm in COVID-19 patients. Even though biosurfactants are naturally formed, they are renowned for their emulsifying abilities in pharmaceuticals and vaccines. Therefore, when combined with traditional antigens for the treatment of COVID-19 disease, these surfactants contain immunological adjuvants that are both non-toxic and non-pyrogenic (Paulino *et al*., 2016). Consequently, these demonstrate that surfactants of biological origin play a significant role as immunosuppressive drugs and may be utilized extensively as a combine therapy toward reducing the inflammatory reactions brought on by coronavirus infection.

BIOSURFACTANTS' ANTI-VIRAL ACTIVITY AGAINST COVID-19

A few biosurfactants cause physiochemical processes that render viruses inactive (Vollenbroich *et al*., 1997). Generally, it is claimed that biosurfactants destroy the virus's envelope and the viral membrane's structures (Shah *et al.*, 2005). The biological surfactant's hydrophilic properties are caused by the acetyl groups, which encourage antiviral action (Borsanyiova *et al.*, 2016). Additionally, the hydrophobic properties with a particular amount of carbon atoms neutralize the virucidal actions (Kracht *et al.*, 1999). High viral inactivation was experienced for surfactants having fatty acid chain longer than fifteen carbon atom; same was reported for monomethyl esters in the semliki forest virus (Kracht *et al.*, 1999). The activity of biological surfactants against coronavirus has been confirmed, and patents on several viruses have been secured (Bonvial *et al.*, 2009; Gross *et al.*, 2014; Gross *et al.*, 2004; Borzeix, 1999; Gross and Shah, 2007). Since SARS-CoV-2 is an enveloped virus, it is possible to apply the evidence from these experiments to it, and the following mechanism of action has been described.

The functional groups of biosurfactants interact with the cell membrane of the virus as the virus enters the host cell and move into bilayered lipid membrane, changing the permeability by either forming ion channels or disrupting the membrane system (Subramaniam *et al.*, 2023). High concentrations of BSs cause the capsid and its surrounding envelope to completely disintegrate (Sarangi *et al.*, 2023). The spike protein and lipid envelope disturbances are enclosed into micelles, which renders the virus inactive (Nitschke and Marangon, 2022). The created micelle has the capacity to serve as carrier that could transport the medication to the site of infection while also providing protection under risky circumstances (Nakashini *et al.*, 2009). Therefore, the ability of biosurfactants to form micelles would make them efficient drug delivery agents for the treatment of covid-19 infection. Additionally, it inactivates the effects of the virus before adsorption or penetration but does not alter viral reproduction.

DESIRABLE PROPERTIES AND BENEFITS OF BIOSURFACTANTS AS ANTI-CORONA VIRUSES

As a more effective means of taking preventative measures or receiving treatment for the SARS-CoV-2 infection, recommendations of some benefits that will be derived when biosurfactants are used will be made in this paper.

1. Surfactants of biological origin should be used for various of purposes in industries including food, medicine, cosmetics, detergents, pharmaceuticals and others. However, its ability to reduce inflammation might be a novel approach to various ways of treating infections due to coronavirus

2. Hand hygience could serve as shield from virus. A more effective defence in preventing viral infection is the use of biosurfactants-encoded handwash or hand sanitisers.

3. The amphiphilic properties of the biosurfactant make it simpler to interface with the lipid bilayer of SARS-CoV-2 and would allow for the easy clearance of the virus by allowing the destruction of the viral DNA.

4. Because of their strong propensity for medication distribution, BSs are particularly well-suited for the job. Because they have a protective antiviral and anti-inflammatory potentialagainst the SARS-CoV-2 virus, it is highly advised to utilize or produce any drug from BSs in addition to conventional medications or vaccinations.

5. Incorporating some therapeutic plants (i.e when using herbal preparations) with microbial surfactants has great promise for effectively removing the viral burden from the human body.

CONCLUSION

The use of biosurfactant as anti-inflammatory in COVID-19 patients, as well as anti-viral agent in the inhibition of viral replication can serve as a potential source of treating Covid 19 where natural compounds produced by microorganisms have shown to have anti-inflammatory and anti-viral properties. The potential of biosurfactants as anti-inflammatory and anti-viral agents against COVID-19, and their potential applications in the management of this disease is promising.

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