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Application of Biosurfactants in the Medical Field

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Abstract

It is generally known that both chemical substances and many kinds of microorganism can be used to produce surfactants or surface-active compounds. Surfactants derived from microorganisms are called biosurfactants, or bio-surface active compounds. Recently, biosurfactants have become more interesting because of their advantages, such as less toxicity and more degradability, which cannot be found in traditional surfactants. Biosurfactant production faces some problems, such as a high cost of production. In the medical field, biosurfactants are attractive, because the products from biosurfactants can be used effectively in small amounts. This can compensate for the high cost of production. In addition, there have been many great discoveries of biosurfactants in the medical field.

Keywords: Biosurfactants, Antimicrobial, Antiviral, Anti-mycoplasma, Anti-tumor, Anti-inflammatory

Introduction

Surface-active compounds can be produced by many kinds of microorganisms instead of being synthesized by chemical substances alone [1-3]. These microorganisms can produce less toxic and more degradable novel biosurfactants, which chemical surfactants are not able to do [4-6]. The surface tension in liquid and the interfacial tension between different liquid phases at the interfacial boundary between phases can be decreased by a molecular interfacial film released from biosurfactants [7-9]. A surfactant consists of 2 parts in its one molecule, the hydrophilic moiety and the hydrophobic moiety [2,8,10]. The former can match with the solution or hydrophilic phase, whereas the latter can match to the hydrophobic phase (oil phase) [11-14]. Emulsification, foaming, wetting, cleansing, phase separation, surface activity, and reduction of the thickness of crude oil are also included in those features as interesting functional properties [14]. It is difficult to produce them on a large scale, but some alternative materials and applications in some fields can ease matters, especially in application aspects [15,16].

The potential applications of biosurfactants and their main mechanisms in interaction will be discussed as related to the medical field and in developing an alternative effective therapy for treating patients.

General biosurfactant properties and functions

Industrial applications of biosurfactants are very interesting, and their physicochemical and biological properties are increasingly studied [17,18]. The significant biological performances of

biosurfactants make them more and more valuable in many fields of industry. Because of that, new biosurfactants and their biological and chemical properties have been widely and intensely researched [5,12,18]. The basic biosurfactant property has been widely known to lower liquid surface tension, which can be simply tested by the methods of drop collapsing and oil displacement tests. Concentration from 72 to less than 30 mN/m is the standard of biosurfactants to reduce surface tension between pure water and air. For instance, the surface tension of water can be reduced by surfactin and rhamnolipids from 72 to 27 mN/m, which is near to minimum detectable value, by a concentration of only 10 μM [2,15,19]. Surface tension can be reduced 33 mN/m by sophorolipids [19] and less than 30 mN/m by mannosylerythritol lipids [20].

Concerning the properties and functions of biosurfactants in the medical field, there are many kinds of original microorganisms, and new ones causing diseases have emerged continuously every year while, during the past few decades, there has not been the discovery of new effective chemical antibiotics at all [10]. Diseases have become strongly resistant to traditional antibiotics, and biosurfactants are novel alternatives in this matter (**Figure 1**). The practical structures and potential biological activities of these microbial surface active compounds are the value answers to the above problems [21]. Biosurfactant has the potential to be used as the antimicrobial performer in medical field as cited relevant report [17]. Moreover, it can also be used as effective therapeutic agent [17,18].

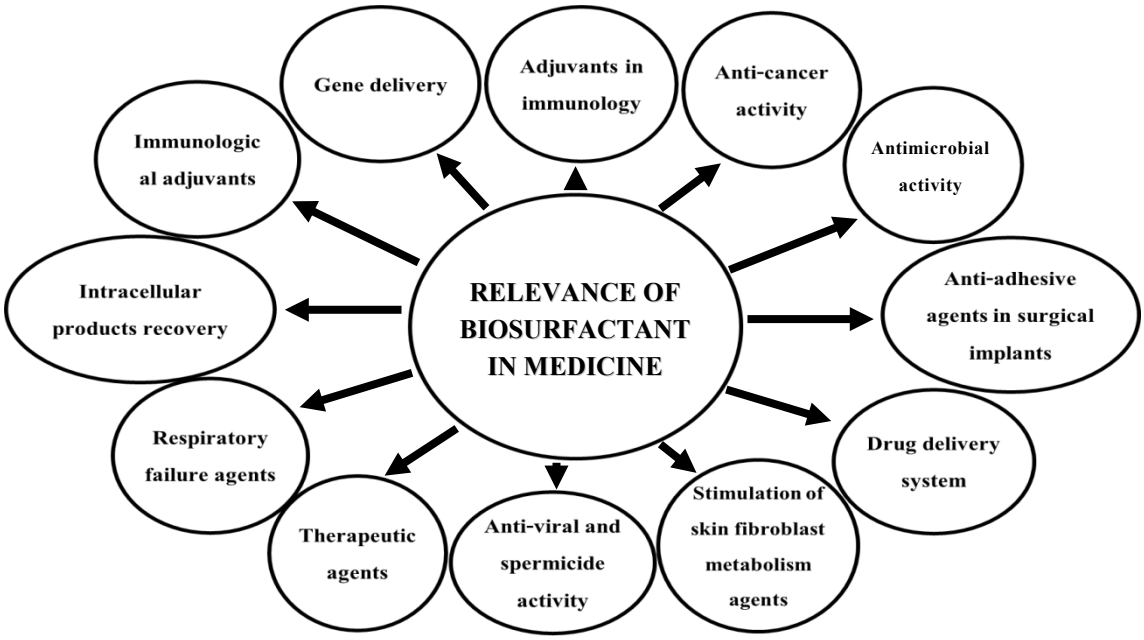

Figure 1 Multifunctional prospective of biosurfactants in the medical field

Antibacterial performance of biosurfactants

For the ability of their molecules to self-associate and form a pore-bearing channel, or micellular aggregation, inside a lipid membrane, upon which their antibiotic activity depends, lipopeptides are considered as the most potentially useful antimicrobial agents [11,22] (**Table 1**). For instance, surfactin has many biological and physical actions, such as antibacterial, antifungal, antitumor, antiviral, and anti-mycoplasma and inflammatory effects, and anti-platelet and hemolytic activity features [15]. The sequence of the hydrocarbon chains is affected, and the membrane thickness is varied, by its activity in penetrating into the membrane through hydrophobic interactions [23]. These activities are nonspecific

modes of action, and are useful for acting on different cell membranes, either Gram-positive or Gram-negative bacteria [24]. This means such performance of surfactin as a lipopeptide is on membrane integrity, rather than other important cellular processes, and could make up the next antibiotic generations [13].

Not only surfactin, but marine *Bacillus circulans* biosurfactant, can also be relied on for antimicrobial performance against several Gram-positive and Gram-negative pathogenic and semi-pathogenic bacteria. *Micrococcus flavus*, *Bacillus pumilus*, *Mycobacterium smegmatis*, *Escherichia coli*, *Serratia marcescens*, and *Proteus vulgaris* are also included in the said effective performers [25]. The chemical structures of these kinds of biosurfactant fractions are overlapping patterns, such as that of surfactin lipopeptides and lichenysin. Furthermore, the observation was made of mild antimicrobial action against methicillin-resistant *Staphylococcus aureus* (MRSA) and other multidrug-resistant (MDR) pathogenic strains [17]. This confirms that biosurfactants can be possibly used as drugs in antimicrobial chemotherapy because of their non-hemolytic nature [8].

There has been recently a study by Huang *et al.* [26], which found that surfactin and polylysine could be significantly used against *Salmonella enteritidis* in dairy products. After having used a response surface methodology, it was found that the minimum inhibitory concentrations of 6.25 surfactin and 31.25 ug/ml polylysine influenced *S. enteritidis*. He also found that *S. enteritidis* was reduced by 6 orders of magnitude at a temperature of 4.45 ºC, with an action time of 6.9 h, and concentration of 10.03 µg/ml at the ratio 1:1 of surfactin/polylysine.

Not only surfactin, but also a large bioactive peptide spectrum with effective potential for applications in biomedical fields, can be produced by *Bacillus subtilis* strains. These are fengycin, surfactin [27], and the iturin congeners, such as iturins, mycosubtilins, and bacillomycins [28]. These are actually membrane-active compounds and amphiphilic surfaces with significant antimicrobial performances. Surfactin and fengycin mainly compose a lipopeptide antimicrobial surfactant produced from *B. subtilis* fmbj strain, also reported to be able to inhibit endospores of *B. cereus* by destruction of the surface structure of the spores, as shown in Transmission Electron Microscopy (TEM) [29].

Bacillus licheniformis, *Bacillus pumilus*, and *Bacillus polymyxa* produced other antimicrobial lipopeptides. For example, polymyxin B from *Bacillus polymyxa* has antibacterial performances against a board spectrum of Gram-negative pathogenic bacteria. It is a cationic agent, and binds to the anionic bacterial outer membrane and leads to a micelle reaction which interrupts membrane integrity [30,31]. *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., *Enterococcus* spp., *Pseudomonas aeruginosa*, and *Acinetobacter* spp. are important nosocomial pathogenic bacteria [32]. They are influenced by polymyxins, and important activities of polymyxins have been reported against *Acinetobacter baumannii*, *Haemophilus* spp., *Pasteurella* spp., *Salmonella* spp., *Shigella* spp., and *Vibrio cholera* [31]. In 2003, the FDA approved Daptomycin (CubicinR) for the treatment of skin infections, which is one of the antimicrobial lipopeptides under commercial development [15]. This practical lipopeptide is synthesized from *Streptomyces roseosporus*, and has great performance against multi-resistant bacteria, such as Methicillin-resistant *Staphylococcus aureus* (MRSA) [33].

Viscosin, a cyclic lipopeptide, produced by *Pseudomonas*, has the property of antimicrobial activity and other significant biological properties [34]. Either rhamnolipids or sophorolipids are in the group of glycolipids, and can perform significant antimicrobial activities [35]. This was used very well against *Bacillus subtilis* with a MIC of 8 ug/ml [36], performed by a mixture of rhamnolipid homologues. There have been reports that Mannosylerythritol lipids (MEL-A and MEL-B) produced by *Candida antarctica* strains that show antimicrobial performance against Gram-positive bacteria [37].

The glycolipids, which have been very recently reported by Nitschke *et al*. [16] in 2010, are rhamnolipids from *P. aeruginosa* LBI. Many bacteria and fungi, such as *Bacillus cereus*, *Escherichia coli*, *Micrococcus luteus*, *Mucor miehei*, *Neurospora crassa, Staphylococcus aureus*, and *Staphylococcus saprophyticus*, could be clearly inhibited by anti-microbial performance by glycolipid biosurfactants [38]. Focculosin was reported by Mimee *et al.* [39] to perform very well, especially against *Staphylococcus* species, including MRSA. The presence of common resistance mechanisms against antibiotic agents, such as methicillin and vancomycin, cannot affect this type of glycolipid, because of its antibacterial properties. *C. albicans* cells could also be eradicated in a very short period of time.

Trehalose lipids, derived from *Tsukamurella* sp. strain DSM 44370, along with trisaccharide and tetrasaccharide lipids, perform some activities against Gram-positive bacteria, with the exception of *Staphylococcus aureus*, the pathogenic bacterial strain. However, they do not really influence Gram-negatives [14].

Table 1 Biosurfactant activity applications in the medical field, type, and microbial sources

Activity	Microorganism	Biosurfactant Type	Reference
Antibacterial	*Actinoplanes friuliensis*	Friulimicin B	[68]
	Bacillus licheniformis	Lichenysin	[69]
	Bacillus pumilus	Pumilacidin	[70]
	Bacillus subtilis	Fusaricidin A, Iturin, Lichenycin, Mycosubtilin, Surfactin, Pumilacidin	[71,72]
	Candida antartica	Mannosylerythritol	[73]
	Lactobacillus	Surfactin	[74]
	Lactobacillus surlactin	Surfactin	[75]
	Pseudomonas aeruginosa	Rhamnolipid	[76]
	Pseudomonas sp.	Amphisin, Entolysin, Massetolide, Putisolvin, Syringomycin, Tolaasin, Viscosin	[77,78]
	Rhodococcus sp.	Trehalose lipid	[79]
	Streptomyces roseosporus	Daptomycin,	[80]
	Rhodococcus erythropolis	Trehalose lipid	[81]
Anti-mycoplasma	*Bacillus subtilis*	Lipopeptide, Surfactin	[82]
Antifungal	*Bacillus subtilis*	Bacillomycin D, Iturin, Iturin A, Surfactin	[83]
Anti-tumor	*Bacillus subtilis*	Surfactin	[83]
	Pseudomonas aeruginosa	Rhamnolipid	[76]
Anti-inflammatory	*Pseudomonas aeruginosa*	mannosyl-erythritol lipid, Surfactin	[84]
Other	*Arthrobacter paraffineu,*	Trehalose mycolates	[85]
	Bacillus licheniformis	Lichenysin	[69]
	Bacillus subtilis	Iturin, Pumilacidin, Surfactin	[82,86,87]
	Candida antartica	Mannosylerythritol	[73]
	Mycobacterium phlei	Trehalose mycolates	[85]
	Mycobacterium tuberculosis	Trehalose dimycolate	[88]
	Micrococcus luteus BN56	Trehalose tetraesters	[89]
	Nocardia erythropolis	Trehalose mycolates	[85]
	Pseudomonas aeruginosa	Rhamnolipid	[76]
	Pseudozyma churashimaensis	Mannosylerythritol	[90]
	Papularia sphaerosperma	Echinocandin	[91]
	Rhodococcu erythropolis,	Glucolipid Trehalolipids, Trehalose mycolates, Trehalose lipid	[85]
	Streptococcus thermophilus	Glycolipid	[92]
	Ustilago scitaminea	Mannosylerythritol	[93]

Antiviral performance of biosurfactants

Surfactin, which is considered the best in medical field applications, can perform effective antiviral activity [11,30] (**Table 1**). From experiments *in vitro*, surfactin and fengycin from *B. subtilis* could significantly inhibit the activities of cell-free virus stocks of many viruses, such as the porcine parvovirus, the pseudorabies virus, the Newcastle disease virus, and the bursal disease virus. They were also able to inhibit infections and the replication of these viruses [40].

Surfactin was suggested as showing antiviral action because of physicochemical interactions between the virus lipid membrane and the membrane-active surfactant. This causes permeability changes and, at higher concentrations, finally results in the disintegration of the membrane system through a micelle effect [41]. Moreover, the feline calicivirus, herpes simplex virus, murine encephalomyocarditis virus, Semliki Forest virus, simian immunodeficiency virus, suid herpes virus, and vesicular stomatitis virus were found to be affected by surfactin. Pumilacidin A, B, C, D, E, F, and G were found to be produced by Gram-positive *Bacillus pumilus* cells. Those pumilacidins have significant antiviral performance against herpes simplex virus 1 (HSV-1), inhibitory activity against H^+, K^+-ATPase, and high protection against gastric ulcers [30], probably through inhibiting the microbial activity that contributes to these ulcers [13].

Sophorolipids are also reported to perform against the human immunodeficiency virus [42]. Trehalose dimycolate and therapeutic drug monitoring in the group of trehalose lipids were shown to be highly resist to intranasal infection caused by the influenza virus in mice, even though a proliferation of T-lymphocytes bearing gamma/delta T-cell receptors was induced, along with the maintenance of acquired resistance to infection [14]. Another lower molecular mass compound against virus is the rhamnolipid alginate complex. Herpes simplex virus types 1 and 2 were affected by rhamnolipid alginate complex, especially the herpes virus cytopathic effect in the Madin-Darby bovine kidney cell line, by a concentration lower than the critical micelle concentration [43].

Anti-mycoplasma performance of biosurfactants

There have been reports of the significant anti-mycoplasma effect of surfactins (**Table 1**). Mycoplasma contamination often happens in cell culture and causes strong limitations to biomedical research, especially as it destroys cell lines. From the studies, surfactin could heal the mammalian cells which have been contaminated with mycoplasmas. They enable the activation of mycoplasmas without any negative effects on cell metabolism in the medium [44]. Furthermore, mycoplasma has also been reported to be eradicated by surfactin from an extensively infected irreplaceable hybridoma cell line [45]. Though the possible use of surfactin in achieving total decontamination is apparently indicated, it was reported that, at various cell intensity and contact times, surfactin was toxic to the infected hybridoma cells. Thus, the best choice is that the initial tests should be performed again to consider if the cytotoxicity of surfactin takes effect before decontamination.

There was another study which reported that surfactin could eliminate the mycoplasma cells of the target cell alone, which is better than that of prevailing antibiotics [1]. In addition, surfactin has been reported to affect *synergistic* effects in combination with enrofloxacin, and achieve mycoplasma-killing performance of about 2 orders of magnitude more significant than if the molecules were used separately.

Antifungal performance of biosurfactants

It has been noted for a long time that biosurfactants can perform antifungal activities, though there have been small numbers of performance against human pathogenic fungi investigated [46] (**Table 1**). Various pathogenic yeasts, along with human mycoses, including *Candida* spp., *Colletotrichum gloeosporioides*, *Corynespora cassiicola*, *Cryptococcus neoformans*, *Fusarium* spp., *Fusarium oxysporum*, *Rhizoctonia* spp., *Trichophyton rubrum*, and *Trichosporon asahii*, were highly inhibited *in vitro* antifungal performance by biosurfactants [35,38]. In tests under acidic conditions, this microbial compound could significantly inhibit all the pathogenic strains and perform synergistic activity with amphotericin B without any cytotoxicity while acting against human cell lines. Nevertheless, there have

been some recent reports that *P. flocculosa* has flocculosin as a nutrient source if it faces difficulty in finding nutrients. Under alkaline conditions, the molecule is rapidly deacylated, and is not able to perform antimicrobial activity. That means that the antimicrobial activity of these glycolipids is open to question [39]. There have also been other antifungal activities of biosurfactants recently demonstrated. These could perform against phytopathogenic fungi, such as lipopetides [11,35], rhamnolipids, and glycolipids [47]. The major mode of action of biosurfactants on fungal pathogens is the direct lysis of zoospores generated by the intercalation of biosurfactants via plasma membranes of the zoospore that are independent of a cell wall [47].

Anti-tumor performance of biosurfactants

From recent demonstrations, some microbial compounds or biosurfactants, considered by cell differentiation, cell immune response, and signal transduction, could control various mammalian cell functions [48] (**Table 1**). It was reported that apoptosis was induced in human breast cancer MCF-7 cells through a ROS/JNK-mediated mitochondrial/caspase pathway by surfactin [49]. The reactive oxygen species (ROS) and Ca^{2+} impact on mitochondria permeability transition pore (MPTP) activity and MCF-7 cell apoptosis induced by surfactin have recently been investigated [50]. The ROS formation which made the MPTP open and the mitochondrial membrane potentially collapse was initially induced by surfactin. This caused an increase in the cytoplasmic Ca^{2+} concentration. Cytochrome C, which activated caspase-9, and eventually induced apoptosis, was also released from mitochondria to cytoplasm through the MPTP [51].

In another study, viscosin, in the group of practical cyclic lipopeptide type biosurfactants isolated from *Pseudomonas libanensis* M9-3, was found to be able to stop the migration of the metastatic prostate cancer cell line, PC-3M, without appearing to have any toxicity effects [34]. Novel cytotoxic activity against cancer cell lines was revealed by lipopeptides, more recently, isoforms of surfactins and fengycins produced by *Bacillus circulans* DMS2, a marine microorganism [52]. There was also the use of lipopeptides in a dose dependent manner as an anti-proliferative performance. After 24 h treatment, more than 90 % inhibition of proliferation on either colon cancer cell lines HCT 15 or HT 29 could be achieved by a concentration of purified lipopeptides of 300 μg/ml.

The selective inhibitory performances of these molecules were assessed after there had been some attempts to study interesting effects against tumor cell lines when comparing them to non-tumor cell lines. *Serratamolide* AT514, in a group of cyclic depsipeptide produced by *Serratia marcescens*, has also been reported as a practical inducer of apoptosis of several cell lines in β-chronic lymphocytic leukemia cells, and in various human tumors. This basically involves the mitochondria-mediated apoptotic pathway, and interferes with Akt/NF-kB survival signals [6]. These biological researches on AT514 with human β-lymphocytes are now progressing towards clinical applications in the field of medical oncology.

Anti-inflammatory performance of biosurfactants

Surfactin plays an important role in this field. For example, from the observation of Byeon *et al*. [53], LPS-induced nitric oxide production in RAW264.7 cells or primary macrophages by inhibition of NF-kB activation could be down-regulated by such bioactive surfactants. The effect of *B. subtilis* PB6, a natural probiotic, on plasma cytokine levels in inflammatory bowel disease and colon mucosal inflammation was also studied [54]. The significant anti-inflammatory performances were the work of surfactin isomers produced by the mangrove bacterium *Bacillus* sp. (No. 061341) especially [55] (**Table 1**). The overproduction of nitric oxide and the release of IL-6 in the LPS-induced murine macrophage cell RAW264.7 could be effectively inhibited by the group of cyclic lipopeptides. The existence of the free carboxyl group in the structure of surfactin the isomer was important to the anti-inflammatory performances, as studied in the relationship of structure-activity. Anti-inflammatory performance in the context of periodontitis caused by *Porphyromonas gingivalis*, the major pathogen of periodontal disease, recently explored by Park *et al*. [56], were induced by the mechanisms which are responsible for surfactin. From observation, pro-inflammatory cytokines, including tumor necrosis factor-a, interleukin

(IL)-1B, IL-6, and IL-12, were effectively reduced by surfactin through suppression of the nuclear factor kB activity in *P. gingivalis* LPS-stimulated THP-1 human macrophage cells, in a Heme oxygenase-1 (HO-1)-dependent fashion. HO-1 expression, a major defense in response to oxidative stress, could also be caused by surfactin therapy. These performances are confirmation that surfactin has crucial properties to prevent caries, periodontitis, and inflammatory diseases.

Immuno-modulatory performance of biosurfactants

From the research of Park and Kim [57], the important therapeutic significations for autoimmune diseases and transplantation, such as allergy, arthritis, and diabetes, were shown by the effective immunosuppressive activities of surfactin (**Table 1**). The production of interleukin-1beta and TNF-alpha cytokines were also activated by a glycolipid complex produced by *Rhodococcus ruber* without modifying the production of IL-6. This means there is a good opportunity to further studies of the antitumor activities and immunomodulating of this biosurfactant [58].

Other biomedical related properties of biosurfactants

There are also many other biomedical-related properties of biosurfactants which can be applied for effective use (**Table 1**). The aggregation of amyloid β-peptide [(AB (1-40)] into fibrils, the main pathological process associated with Alzheimer's disease, was affected by a high surfactin micelle concentration [59]. From the studies of Bouffioux *et al*. [60], Brasseur *et al*. [61], and Francius *et al*. [62], surfactin and its synthetic analogues have the ability to change the nanoscale organization of supported bilayers and to induce nanoripple structures with intriguing perspectives for biotechnological and biomedical applications.

Eeman *et al.* [63] studied the ability of fengycin and found that it interacted with the lipid constituents of the stratum corneum extracellular matrix and with cholesterol. Deleu *et al*. [22] reported that fengycin can also cause membrane perturbations. In Morita *et al*. [64], the cell activating property of mannosylerythritol lipid (MEL) was investigated by cultured fibroblast and papilla cells, and a 3-dimensional cultured human skin model. They found that the ability of the fibroblast and of the papilla cells were clearly increased by the diacetylated MEL (MEL-A) derived from soybean oil over 150 %. Compared with that of control cell increases, it could be used as a new hair growth agent stimulating the papilla cells. Using a 3-dimensional cultured human skin model, it was also observed that the viability of the SDS damaged cells could improve significantly when MEL-A in a dose-dependent manner was added. That means MEL-A also had a ceramide-like moisturizing activity toward skin cells. MEL-B also displayed excellent moisturizing properties, which was equivalent to those of natural ceramides on human skin [65].

It was reported from the study of Zaragoza *et al*. [66] that the swelling of human erythrocytes, followed by hemolysis, was made by a succinoyl trehalose lipid isolated from *Rhodococcus* sp. at concentrations well below its critical micelle concentration. It can be concluded that the hemolysis of human erythrocytes was the consequence of trehalose lipid through a colloid-osmotic mechanism, especially the formation of enhanced permeability domains, or "pores", strengthened by biosurfactant in the erythrocyte membrane. There was also a report from Sanchez *et al*. [67] that *Pseudomonas aeruginosa* dirhamnolipid could induce the permealization of biological and artificial membranes. As indicated by the similar rates of K^+ and hemoglobin leakage, and by the absence of effect of osmotic protectants, the hemolysis of human erythrocytes through a lytic mechanism was caused by *Pseudomonas aeruginosa* dirhamnolipid. The usual disc shape of erythrocytes could be changed with the addition of biosurfactant into that of spheroechinocytes, which was shown through scanning electron microscopy.

Conclusions

Interest in the application of biosurfactants is significantly increasing among researchers throughout the world. Researchers have studied these surface-active compounds and their practical operations, as there are more increases in the demand for new specific surfactants in several fields, such as agriculture, cosmetics, food, and the pharmaceutical and environmental industries. Biosurfactants themselves have been well known as effective and environmentally compatible compounds, so they can completely meet demand. The development of biosurfactant applications on a large scale in various industries has been delayed by the most important factors of the complexity and the high cost of their production. However, effective antimicrobial, anti-adhesive, and immune-modulating performances of these surface-active compounds include many successful uses in medical insertion safety, immunotherapy, and gene therapy. This suggests that there should be further study in these fields. Furthermore, in the pharmaceutical and biomedical industries, the small amounts produced and required can compensate for the high cost of their production. For example, it has been shown that only very low concentrations of biosurfactants will be used as pharmaceutical agents in each application.

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