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Review

Anti-proliferative activity of surfactins on human cancer cells and their potential use in therapeutics

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ABSTRACT

Surfactins are cyclic lipopeptides that are isolated from various *Bacillus* strains. They are made up of heptapeptides and β-hydroxy fatty acids of variable chain lengths of carbon atoms. Therapeutically they are known to inhibit invasion, migration, and colony formation of human breast carcinoma cells. The role of surfactins is also known as anti-proliferative agents against human cancer cells through induction of apoptosis, arrest of the cell cycle, or suppression of survival signaling. The cytotoxic activity of surfactins is also perceived against human chronic myelogenous leukemia cells, human colon cancer cells, and hepatic carcinoma cells. Considering the wide spectrum of targets, the molecular effects of surfactins are diverse in different cancer cells and they can serve as promising chemotherapeutic agents for the treatment of cancer. Surfactins are being delivered to the targeted cancer cells through nano-carriers or nano-formulations. The present review article provides insight on different types and variations of surfactins, their molecular effect on different cancer cells, and their therapeutic use in the treatment of human cancer.

1. Introduction

Surfactins are biosurfactants produced by various *Bacillus* strains during the stationary growth phase of bacteria to survive in adverse conditions [1–3]. They are biosynthesized non-ribosomal in the bacteria cell with the help of non-ribosomal peptide synthase enzymes (NRPS) which recognizes, activates, modifies, and link amino acids to generate peptides [4]. The process of surfactin biosynthesis is regulated by surfactin synthetase enzymes that consist of four open reading frames (SrfA, SrfB, SrfC, and SrfD) [5]. SrfD starts the initial reaction of surfactin biosynthesis which is followed by SrfA, SrfB, and SrfD to form seven modules that contain twenty-four catalytic domains. Each domain works to incorporate one substrate to the developing heptapeptide chain [6,7]. The fatty acyl chain is incorporated into the peptidyl backbone through a lipo-initiation reaction [8]. The genes responsible for the synthesis of non-ribosomal peptide synthase enzymes (NRPS) are encoded by Srf operon [9,10]. Surfactins are amphipathic cyclic lipopeptides that are made up of heptapeptides and beta-hydroxy fatty acids. They have carbonyl terminal end of the peptide being esterified to the hydroxyl group of fatty acid and 3-hydroxy-13-methyl tetra decanoic acid amidated to the N-terminal amine of the heptapeptide moiety. They have the presence of heptapeptide with a chiral sequence (L-Glu-L-Leu--D-Leu-L-Val-L-Asp-D-Leu-L-Leu) linked to a hydroxyl fatty acid through a lactone bond [11] (Fig. 1).

They are known to have different pharmacological activities such as antibacterial, anti-fungal [12], anti-inflammatory [13,14], thrombolytic [15,16], anti-fibrinogenic, anti-mycoplasma [17], anti-hyper cholesterolemic, anti-viral, and anti-cancer [16,18,19] activity. Isoforms of surfactins occur in cells as variants of seven peptides with a distinct chain length of the aliphatic group. They make use of the β-sheet structure of the protein in an aqueous medium to form a horse saddle conformation which provides wide biological activities to the molecule [20]. They dislocate and make the cellular membrane conformation weak by several mechanisms such as solubilization of membrane through the detergent-like mechanism, inclusion into the lipid bilayer, and alteration in permeability of membrane either through the diffusion of ions across the membrane barrier or channel formation [21]. Various research studies have suggested that surfactins act as anticancer agents by interfering with some crucial processes of cancer development. Therefore, the present review article aims to give insight into different types and variations of surfactants, their molecular effect on different cancer cells, and their therapeutic use in the treatment of human cancer.

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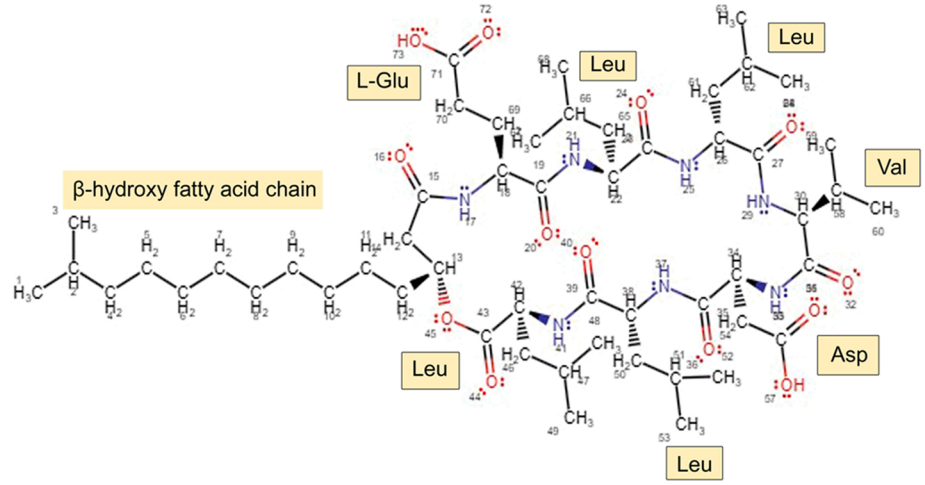
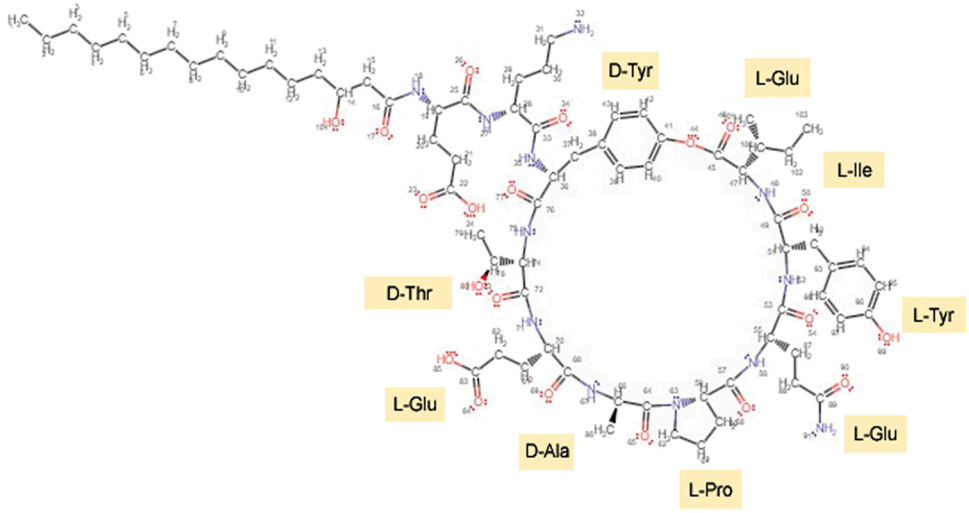
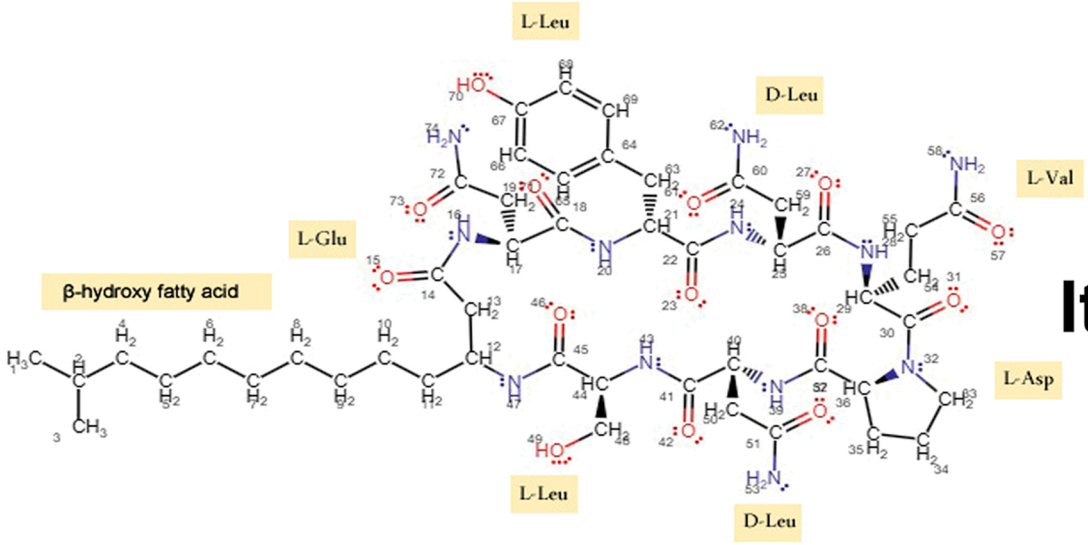


Surfactin



Fengycin



Iturin A

Fig. 1. Structure of Surfactin was prepared by using the Chemical Sketch Tool of Protein Data bank. The isomeric smiles were retrieved from National Center for Biotechnology Information PubChem Compound Summary for CID 443592, Surfactin, CID 443591, Fengycin, CID 102287549, Iturin A.

2. Isoforms of surfactins

2.1. Natural surfactins

The isoforms of surfactins are biosynthesized in various *Bacillus* species such as *Bacillus subtilis, Bacillus velezensi, Bacillus amyloliquefaciens, Bacillus spizizeni*, *Bacillus licheniformis,* and *Bacillus pumillus.* that the standard structure of surfactin is made up of a heptapeptide sequence (L-Glu-L-Leu-D-Leu-L-Val-L-Asp-D-Leu-L-Leu) linked to a β-hydroxy fatty acid with 13, 14 or 15 carbon atoms [22]. The isoform of surfactin which differed from the standard structure of surfactin at the seventh amino acid L-leucine replaced by L-valine in the peptide chain of surfactin was named isoform [Val7] surfactin [23]. Similarly, the isoform of surfactin that had L-isoleucine which replaced L-valine at the seventh amino acid in the peptide chain was named isoform [Ile7] surfactin [24]. In the standard structure of surfactin aspartic acid is present at the 5th position, D-Leucine at the 3rd and 6th positions. However, the lichenysin biosynthesized by *Bacillus licheniformis* differs from standard surfactin by the presence of glutamine as the first amino acid residue instead of glutamic acid. The pumilacidin biosynthesized by *Bacillus pumillus* differs from standard surfactin by the presence of leucine at the 4th position instead of valine and the presence of valine or isoleucine at the 7th position instead of leucine. Surfactins also have diversity on the basis of differences in their fatty acid chain. The length of the fatty acid chain varies from 12 to 17 carbon atoms, especially at C14 and C15 positions. Fatty acid chains also have a difference in their isometry, it can be linear, branched, iso or anteiso. Iso forms of fatty acids are found in all odd or even-numbered carbon chain lengths whereas anteiso forms are found in uneven carbon chain lengths [25]. In previous studies, it is being observed that the surfactin methyl esters are produced by *Bacillus subtilis* HSO121 [26]. Similarly, the presence of methylated surfactin with valine at the 7th position was produced by the bacillus strain isolated from mangrove plants [27]. There was a remarkable difference observed in the surfactin methyl esters produced by *Bacillus licheniformis* HSN221 and *Bacillus pumilus* through lichenysin methyl esters and surfactin methyl esters [28,29]. The natural linear surfactins were also identified in the culture of *Bacillus* strains [30]. From in vitro studies, it was observed that heterologous enzymes (V8 endoprotease) from *Staphylococcus aureus* are able to catalyze surfactins into the linear form [31]. From the in vivo studies on Streptomyces sp., it was observed that linear forms of surfactins were developed in bacteria through hydrolysis done by resistant enzymes [32].

2.2. Chemical modifications in surfactins

The amidation of surfactins can be done through a reaction with alcohol and then with ammonium chloride [33]. Most derivatives of surfactins can be prepared by the esterification process which is helpful in studying interfacial and biological activities [34]. The linear structure of surfactin from the cyclic structure can be prepared by chemical alkaline treatment [35]. Synthetic forms of surfactins were also synthesized by chemical reactions. Initially, diastereoisomers of surfactin B2 were synthesized by the solution method through condensation of active ester and azide fragments [36]. Surfactins and their four analogs were synthesized by solid-phase peptide synthesis using the Fmoc method on Sasrin resin [37]. The linear analogs of surfactins were synthesized by using the solid-phase peptide synthesis method [38]. The changes were made in the fatty acid chain length of surfactins and the crucial role of charge, hydrophobicity, and geometry in controlling the membrane activity of surfactin was observed. Even synthetic analogs of surfactins are better for developing new surfactants with tunable specific properties for biotechnological and medical applications [39].

3. Surfactins production and isolation

3.1. Production from natural resources

Microorganisms that produce surfactins are isolated from samples collected from stressed environments such as halophilic soils, marine water or sediments, diesel or oil-polluted soil, oil reservoir, sea harbor, automobile garage, and other extreme environments [40–46]. The media required for the growth of these microorganisms are the sole sources of carbon, nitrogen, and minerals. The carbon sources required for the growth of these organisms are carbohydrates, oils, and hydrocarbons. Therefore, glucose, sucrose, glycerol, crude oil, or diesel are used in the media as a sole carbon source to maintain the quality and quantity of surfactins [47,48]. The nitrogen sources used for the growth of these organisms are urea, nitrate, peptone, yeast, ammonium sulfate, sodium nitrates, meat, and malt [48,49]. The triphosphate form of phosphate is provided for the better growth of these microorganisms [50]. The environmental factors that affect the production of surfactins in the culture of microorganisms are temperature, pH, oxygen availability, and agitation speed. The temperature required for the production of surfactin varies from 25 ºC to 40 ºC based on the type of microorganism [51]. The thermophilic bacillus sp. requires a temperature above 40 ºC for growth and surfactin production [52]. Alkaline pH (7.5–8) is required to enhance the production of surfactin in the culture [53,54]. The incubation period affects surfactin production because it varies based on different types of microorganisms. The incubation period of 48–120 hrs. is optimum but some organisms require more than 168 hrs. for surfactin production [51,54]. Optimum oxygen availability and agitation are required for better surfactin production in culture media. High agitation reduces surfactin production in the *Bacillus subtilis* culture due to the endospores formation [55].

The techniques used for isolation, purification, and detection of surfactins are centrifugation, column chromatography, ion-exchange chromatography, thin-layer chromatography (TLC), dialysis, lyophilization, and isoelectric focusing [50]. The most commonly used techniques for isolation of surfactins is either through batch mode or continuous mode. The batch mode includes the use of solvents mixtures such as chloroform-methanol, dichloromethane-methanol, ether, butanol, hexane, and acetic acid for extraction of surfactins. The continuous mode utilizes a centrifugation process for the separation of bacteria and crude surfactins. For detection, crude surfactins are separated on a silica gel plate using mobile phase chloroform, methanol, and water. Then, different types of surfactins are characterized by using developing reagents such as ninhydrin or phenol sulfuric acid. For purification of surfactins techniques such as column chromatography, ion-exchange chromatography, dialysis, lyophilization, ultrafiltration, and isoelectric focusing are used [56,57].

3.2. Genetic engineering in bacterial strains to develop specific surfactins

Biosynthetic variants of surfactins are modified to increase the biological activities, reduce the toxicity or increase the solubility in water [25]. Genetically modified Bacillus species were developed to overcome the difficulties involved in the biosynthesis of surfactins. The modifications were made in the genes responsible for the regulation of non-ribosomal peptide synthase enzymes (NRPS) facilitated mechanisms to promote over expression of signaling peptides [58], surfactin transporter, and assistant proteins [59]. The native Psrf promoter was replaced with the IPTG-inducible hybrid promoter Pspac in *B. subtilis* fmbR to increase the yield of surfactins tenfold [60]. The native promoters such as PgroE, PsacB, and PsacP in *B. subtilis* THY-7 were identified using transcriptome analysis, and the limitations of the native srfA promoter were determined. This limitation of the native srfA promoter was eliminated by replacing it with synthetic promoters to enhance the surfactin biosynthesis in *B. subtilis* [61]. The gene (codY) which negatively regulates the bkd operon and in turn increases the surfactin

production by 5.8 fold in *B. subtilis* BBG258 was identified [62]. The CRISPR interference technology was used to repress the bkdAA and bkdAB genes of the bkd operon to improve surfactin production [63].

4. Anti-proliferation properties and mode of action of surfactins on human cancer cells

The lipopeptides isolated from marine *Bacillus circulans* DMS-2 have significant anti-proliferation activity against the human colon cancer cell lines HCT-15 and HT-29 [64]. The biosurfactants produced by the Dematiaceous Fungus *Exophiala dermatitidis* SK80 have anti-proliferative activity against cervical cancer (Hella) cells and leukemia (U937) cells [65]. Inhibition in the growth of MCF-7 human breast cancer cells was observed in a dose-dependent manner when treated with three isoforms of surfactins isolated from the culture of *Bacillus subtilis* CSY191 strains [66]. The cyclic lipopeptide bacillomycin D produced by *Bacillus amyloliquefaciens* strain fiply 3 A inhibits the human cancer cell lines such as alveolar adenocarcinoma (A549), renal carcinoma (A498), and colon adenocarcinoma (HCT-15) by inducing apoptosis [67]. Pseudofactin II (PFII) is a cyclic lipopeptide biosurfactant isolated from the Arctic strain of *Pseudomonas fluorescens* BD5 and has the ability to induce apoptosis in A375 melanoma cells [68]. The biosurfactins produced by *Bacillus safensis* F4 have antitumor activity against T47D breast cancer cells and B16F10 mouse melanoma cells [69]. The five surfactin isomers isolated from *Bacillus pumilus* strain HY1 have the potential to inhibit the proliferation of cancer cell lines MCF-7 and Caco-2 [70].

The surfactins inhibit the activation of extracellular related protein kinase and phosphoinositide-3-kinase or Akt to arrest the cell cycle and induce the pro-apoptosis process in human colon cancer (LoVo) cells [71] (Fig. 2). Fengycin isolated from the culture of *Bacillus subtilis* fmbj shows inhibition in the proliferation of human colon cancer HT29 cells through cell apoptosis and interfering with cell cycle processes by targeting the Bax/Bcl-2 pathway [72] (Fig. 3). The iturin A-like lipopeptides produced by *Bacillus subtilis* inhibit proliferation of heterogeneous human epithelial colorectal adenocarcinoma (Caco-2) cells by inducing paraptosis and apoptosis [73] (Fig. 4). The surfactin mono-methyl ester was isolated from the culture of *Bacillus subtilis* HSO121 and its anti-tumor activity on Hella cell lines was studied. It was suggested that the anti-tumor activity of surfactins on Hella cell lines was due to the presence of the Glu residues of surfactins-like lipopeptides [26]. The Surfactin C-15 has the ability to form nano-micelles and can arrest the growth of human cervix cancer Hella cells in a dose-dependent manner [74].

Surfactins isolated from *Bacillus natto* TK-1 induces apoptosis in human hepatoma (HepG2) cells through an increase in reactive oxygen species (ROS) production that causes endoplasmic reticulum stress (ERS) which leads to an increase in the $[Ca^{2+}]i$ level and starts the processes associated with blocking of the extracellular signal-regulated kinase (ERK) pathway [75]. Surfactins isolated from the *Halomonas nitroreducens* inhibit the proliferation of hepatocellular carcinoma (HepG2) cells through induction of apoptosis and G2/M arrest [76] (Fig. 2). The cyclic lipopeptides (CLP) isolated from *Bacillus subtilis* natto T-2 inhibits the proliferation of human leukemia K562 cells through cell cycle arrest at the G1 phase and it induces apoptosis in human leukemia K562 cells through caspase-3 and poly (ADP-ribose) polymerase (PARP) [77]. The cyclic lipopeptide inhibits proliferation and induces apoptosis in human leukemia K562 cells through an increase in $[Ca^{2+}]i$ that evoked ERK phosphorylation which subsequently activates Bax, cytochrome c, and caspase-3 [78] (Fig. 2). The iturin produced by *Bacillus subtilis* has the potential to inhibit chronic myelogenous leukemia by inducing paraptosis, apoptosis, and inhibition of autophagy in K562 myelogenous leukemia cells [79] (Fig. 4).

The surfactins isolated from *Bacillus subtilis* have the potential to induce apoptosis in human oral squamous carcinoma cells through the production of reactive oxygen species (ROS) which leads to the activation of the mitochondrial pathway [80]. Surfactins induce autophagy in human oral squamous carcinoma cells by sharing regulatory signals with the apoptosis pathway. It also arrests the cell cycle at the G_2/M transition through the accumulation of p53 and p21 which inhibits the activity of cyclin B1 and $p34^{cdc2}$ through ROS derived from NADPH oxidase [81] (Fig. 2). Fengycin decreases the proliferation of human lung cancer cells through cell cycle arrest at the G0/G1 stage of the cell cycle by downregulating cyclin D1 and cyclin-dependent kinase 4 (CDK4) activity. It triggers apoptosis in the human lung cancer cells through the mitochondrial pathway with increased caspase activity, Bax expression, and cytochrome C release in to the cytoplasm and decreases the level of Bcl-2 [82] (Fig. 3).

The surfactins isolated from the *Bacillus subtilis* natto TK-1 strain has the ability to inhibit the proliferation of human breast cancer MCF-7 cells through apoptosis and cell cycle arrest. The apoptosis was induced in the human breast cancer MCF-7 cells through elevation of $[Ca^{2+}]i$ and cell cycle arrest at G1/M transition was due to the accumulation of the tumor suppressor p53, cyclin kinase inhibitor p21waf1/cip1, and inhibition of the activity of G2 specific kinase, cyclin B1/p34cdc2 [83]. The surfactins induce the generation of reactive oxygen species in human breast cancer MCF-7 cells that initiate the phosphorylation of ERK1/2 and JNK which in turn results in the initiation of apoptosis through the mitochondrial / caspase pathway. It increases the Bax-to-Bcl-2 expression ratio, loss of mitochondrial membrane potential, cytochrome c release, and caspase cascade reaction [84]. The surfactins induce apoptosis in human breast cancer MCF-7 cells by increasing the ROS formation and leading to the mitochondria

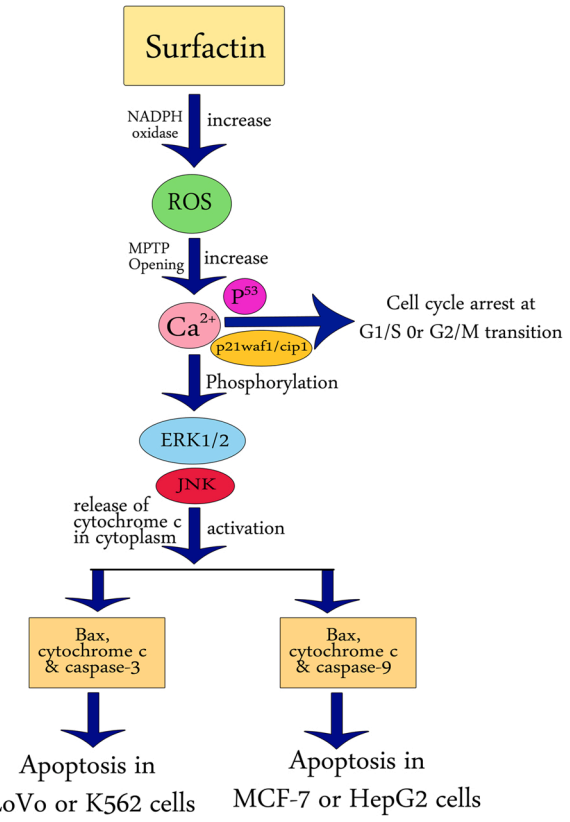


Fig. 2. Shows the mode of action of surfactins on different human cancer cells. it increases ROS level in cells through NADPH oxidase that opens the mitochondria permeability transition pore (MPTP) which in turn increases Ca2+ ions concentration and starts phosphorylation of ERK1/2 and JNK. Simultaneously, there is the accumulation of P53 and p21waf1/cip1 which inhibits the activity of cyclin B1/p34cdc2 to arrest the cell cycle at the G1/S or G2/M phase. This results in the release of Cytochrome C in cytoplasm and activation of Caspase-3 or Caspase-9 to induce apoptosis in cells.

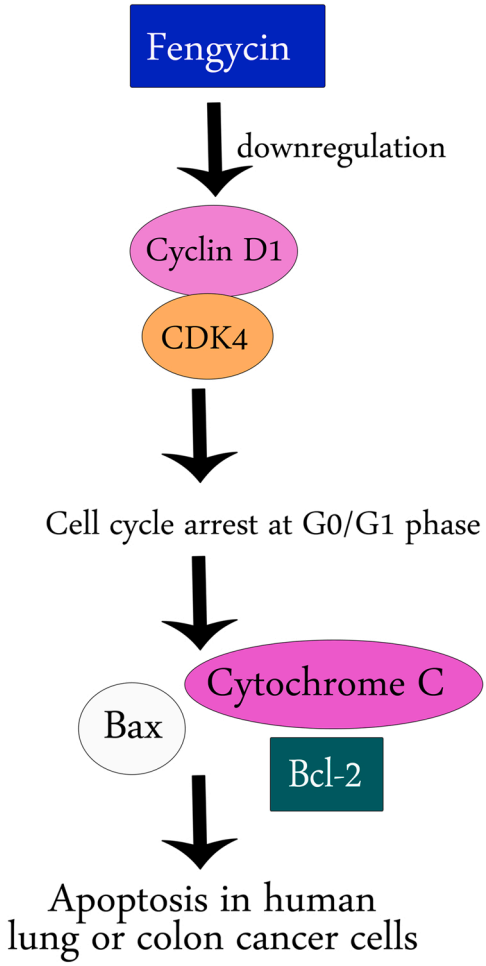


Fig. 3. Shows the mode of action of fengycin. it downregulates the activity of CDK4 and cyclin D1 and arrests the cell cycle at G0/G1 phase. It induces apoptosis through a mitochondrial pathway with the increase in caspase activity, Bax expression, and cytochrome C release into the cytoplasm and a decrease in the level of Bcl-2.

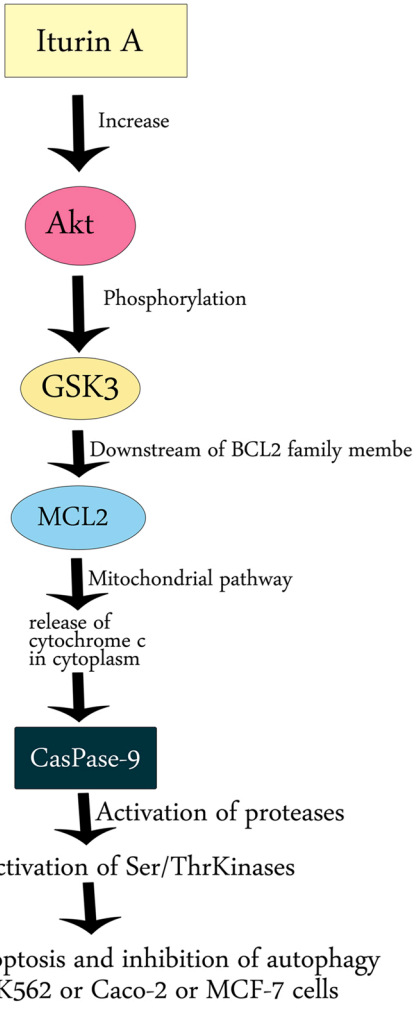


Fig. 4. Shows the mode of action of iturin on different human cancer cells. (MCF-2, Caco-2 & K562 myelogenous leukemia cells). it increases the Akt level in cells which in turn phosphorylates isoforms of GSK3 ((GSK3-S21, GSK3-S9). This causes downregulation of BCL2 family member MCL2 in the Mitochondrial pathway which results in the release of Cytochrome C in the cytoplasm and activation of Caspase-9. it induces activation of various proteases which inactivates ser/thr kinases and induces apoptosis in cancer cells.

permeability transition pore (MPTP) opening. This was accompanied by the collapse of mitochondrial membrane potential and then an increase in [Ca^{2+}] I concentration which changes the mitochondrial permeability to release the cytochrome C to the cytoplasm through MPTP to activate caspase-9 [85] (Fig. 2).

The lipopeptides produced by *Bacillus subtilis* HSO121 inhibit the proliferation of Bcap-37 cell lines by inducing apoptosis through a significant decrease in the unsaturated degree of the cellular fatty acids which, in turn, disturbed the fatty acid composition in the cell membrane [11]. Surfactins inhibit the proliferation of human breast carcinoma cells by inhibiting the expression of protein Matrix Metallopeptidase-9 (MMP-9) through suppression of the NF-kB, AP-1, phosphatidylinositol 3-kinase (Pi-3 K)/Akt and the ERK signaling pathways [86]. The proliferation of human breast cancer cells can be inhibited through cell cycle arrest at the G1 phase by surfactin produced by *Bacillus subtilis* 573 and glycoproteins produced by *Lactobacillus paracasei* A20 [87]. The Marine lipopeptide Iturin A isolated from the marine bacterium *Bacillus megaterium*, induced apoptosis in human breast cancer cells through Akt-mediated GSK3β and βα FoxO3a signaling [88] (Fig. 4).

5. Surfactins in drug delivery and their therapeutic use

Various types of nanocarriers such as liposomes, polymeric nanoparticles, niosomes, micelles, solid lipid nanoparticles, dendrimers, gold nanoparticles, protein nanoparticles, nanotubes, micro or nanoemulsions, and magnetic nanoparticles can be utilized to deliver surfactins for therapy [89]. The nano-formulations of surfactins are good sources due to high drug loading capacity, better cancer cell targeting, prolonged circulation time in blood, improved bioactivity, and easy-to-manipulate release of drug [90]. The nano-formulations are capable to accumulate at the cancer sites through the enhanced permeation and retention (EPR) effect [91]. The nano-formulations carrying surfactins should be coated with hydrophobic polymer to avoid the opsonization and then get recognized by the reticuloendothelial system (RES) which clears it out of the body [92]. The nano-formulations carrying surfactins should be surface modified with target ligands which will deliver a high amount of surfactin-loaded nano-formulation towards cancer cells than normal cells due to their high affinity towards overexpressed receptors on cancer cell surfaces [93]. Thus, the collective effect of EPR and ligand receptor binding increases the concentration of surfactins in cancer cells and improves the efficiency of treatment. Modification of nano-carriers by formulating surfactins with polymers can protect the drug from premature release, the dose of the drug is released slowly and curbs the hemolytic side

effect of surfactin [20] (Wu et. al. 2017).

The somocystinamide A (ScA) loaded liposomes induce cytotoxicity in various cancer cell lines. It alters the lipid compartment of cells by forming ceramide and its accumulation in turn results in the induction of Caspase B for apoptosis [94]. The non-ionic surfactant-based vesicles (niosomes) were developed using different surfactants such as span 20, tween 20, span 60, span 40, brij 76, brij 78, and brij72 by the film hydration method. They tested the efficiency of niosomes to protect Paclitaxel (PCT) against different gastrointestinal enzymes such as pepsin, trypsin, and chymotrypsin through oral drug delivery. They observed that the gastrointestinal stability of Paclitaxel (PCT) was well preserved with Span 40 niosomes [95]. The three types of surfactant templated mesoporous silica nanoparticles of 150–660 nm in diameter were developed that exhibited the high drug loading capacities, long-term and high anticancer efficacy and sustainable release profiles in MCF-7 cells [96]. the properties of polymer-coated magnetic nanoparticles for drug delivery application were compared and suggested that the polymer-coated magnetic nanoparticles made with PF127 as a surfactant (PMNPs-PF127) has excellent uptake, cytocompatibility, and drug release capability as compared to the polymer-coated magnetic nanoparticles made with SDS as a surfactant (PMNPs-SDS) [97].

A novel surfactant to improve the solubility of a water-insoluble anticancer drug was synthesized to evaluate its effect on endothelial cells. From MTT and LDH assays on endothelial cells, it was concluded that the surfactant has a promising drug delivery system to solubilize anticancer drugs through their self-assembling ability into spherical, cylindrical, or lamellar structures [98]. The block ionomer complexes (BIC) formed from the polyethylene glycol and poly-4-vinyl benzyl phosphonate (PEG-b-PVBP) and many cationic surfactants have the capability to load high amounts of anti-cancer drugs (doxorubicin), high stability against dilution and changes in ionic strength. The drug release is slow from block ionomer complexes (BIC) at alkaline pH as compared to acidic pH in MCF-7 breast cancer cells and induces a cytotoxic effect in cells [99]. The novel poly-L-asparagine (PASN) nano capsules involve the use of cationic surfactant as a bridge for the interaction of PASN with the lipid core of cancer cells. These nano capsules loaded with anticancer drugs interacted with the NCl-H460 human cancer cells and induced cytotoxicity in them [100]. The water-dispersible nanoparticles were developed from irinotecan hydrochloride and 7-ethyl-10 hydroxy camptothecin which displayed high bioavailability and anti-cancer activity [101].

The surfactins-based nanocarriers loaded with doxorubicin (DOX) induce strong cytotoxicity against DOX-resistant human breast cancer MCF-7/ADR cells by accumulating more efficiently in tumors as compared to free DOX [102]. in vitro, cytotoxic studies suggested that cationic or anionic surfactant mixtures have the self-assembling ability which can effectively work as nanocarriers for drugs [103]. The doxorubicin-loaded vesicles harbor the potential for phase delivery, prolonged treatment, and even on-demand release to induce cell death in cancer cells. The starch nanoparticles were developed using acid hydrolysis (SNP-H) and ethanol precipitation method (SNP-P) which were modified using surfactants (CTAB, SDS, and Tween-20). Among the two starch nanoparticles, CTAB modified SNP-H had high drug loading capacity and sustainable release of drug at pH 5.8 and 7.4 [104]. The cytotoxicity assay suggested better biocompatibility of nanoparticles with 7F2 cells. Saponins have high surface activity, self-assembly, and improved drug solubility and bioavailability properties [105]. Hence, it can be a better source for drug delivery but further studies are required to fulfill the limitations such as applicability, hemolysis, development of technology, and in-depth molecular mechanism of saponins as drug delivery system carriers.

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