# STAPHYLOCOCCINS: THEIR APPLICATIONS AND FUTURE PERSPECTIVE

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## ABSTRACT

*Bacteriocins are the ribosomally synthesized peptides synthesized by bacteria which have antagonistic activity against other bacteria. Staphylococcins, are the bacteriocins produced by Staphylococcus spp., have various applications due to their effectiveness against a wide variety of bacteria. The future perspective of their application includes their use in cancer treatment, in skin infections, as food biopreservative, in nosocomial infections etc.*

**Key-Words: Staphylococcins, biopreservatives, bacteriocins.**

## INTRODUCTION:

Staphylococci are the bacteria which are generally divided into two main groups, coagulase-positive staphylococci (CPS) and coagulase-negative staphylococci (CNS) and this categorization is based on the production of coagulase, an enzyme-like factor that causes fibrin to clot, which is generally associated with pathogenicity (Bannerman and Peacock, 2007). The bacteriocin produced by *Staphylococcus spp*. are collectively known as staphylococcins. The first citation about bacteriocin-like antagonism between Gram positive bacteria was reported by Babes in 1885. He described staphylococci could inhibit the growth of other bacteria on solid medium, whereas the term staphylococcin was created later in 1946 (Fredericq, 1946).

Bacteriocins are classically defined as ribosomally synthesized proteinaceous compounds with bactericidal activity against other bacteria (Jack et al., 1995; Heng et al., 2007). The strains producing bacteriocin have developed a protection system against their own bacteriocin, named immunity. Each bacteriocin producing strains has its immune system, which is generally expressed concomitantly with the bacteriocin structural genes (Jack et al., 1995; Heng et al., 2007). The ribosomal synthesis of the bacteriocins and the presence of an immunity system

differs it from the other antimicrobial substances such as antibiotics (Jack et al., 1995). A revised classification scheme for bacteriocins based on their biochemical characteristics has been proposed by Heng and coworkers (Heng et al., 2007) which is a modification of the classification scheme presented by Cotter *et al.* in 2005(Cotter et al., 2005). According to the classification of the bacteriocins, the bacteriocins can be divided into four classes. Class I and Class II are the most studied bacteriocins with better elucidated mode of action and possess industrial and clinical applications (Jack et al., 1995; Heng et al., 2007 and Cotter et al., 2005).

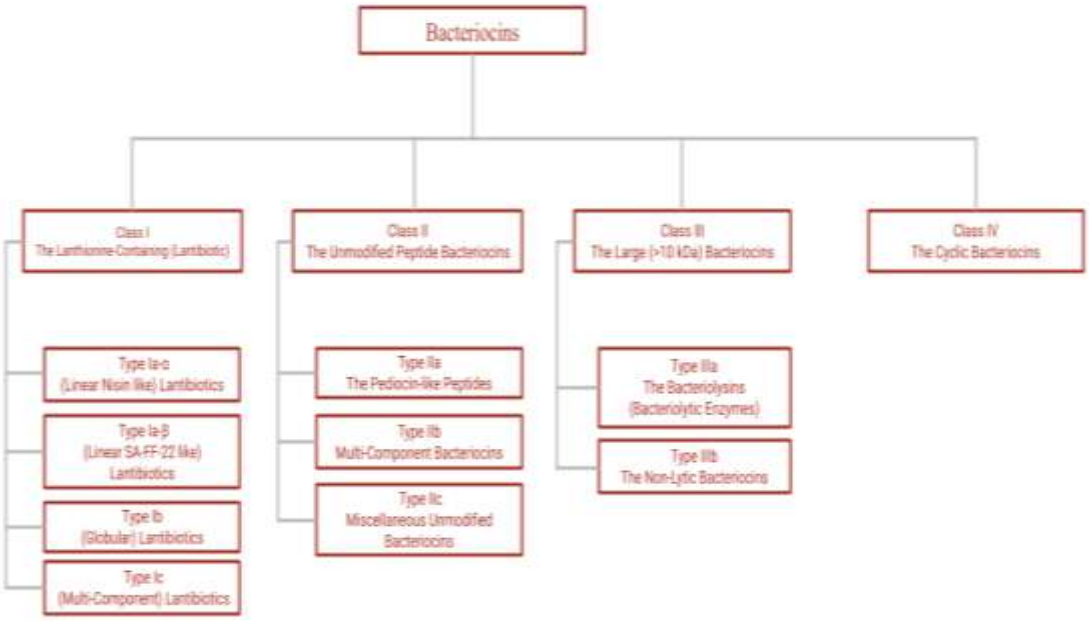


*Figure: Classification of Bacteriocins. (Heng et al., 2007)*

Staphylococcins are the bacteriocins which can inhibit many bacterial species including several bacterial pathogens and thus possess potential practical applications.

1. **Staphylococcins produced by Coagulase- negative Staphylococci**: The best characterized staphylococcins produced by CPS are class I lantibiotics. The lantibiotics are unique as these are produced on the ribosome as a prepeptide which undergoes extensive post translational modification to form the biologically active peptide with the modification of the amino acids Ser, Thr and Cys residues. Lantibiotics have a high proportion of unusual amino acids which are made by biosynthetic pathways which require novel modification enzymes (Papaggianni, 2003; Sahl et al., 1998 and McAuliffe et al., 2001).

a. Epilancin K7 and its variants Epilancin K7 is a lantibiotic which is produced by *S. epidermidis* K7 (Pulverer et al., 1976).

*b.* Epidermin and its variants epidermin are the most frequently produced lantibiotics in the group of CNS, being reisolated from many strains of *S. epidermidis* and also from other staphylococcal species (Bierbaum et al., 1996).

*c.* Gallidermin which is produced by *S. gallinarum* DSM4616, is a natural epidermin variant which is a lantibiotic (Kellner et al., 1988).
*d.* Nukacin ISK-1 which was isolated from a bacterial strain from well aged Nukadoko, a bed of fermented rice (Kimura et al., 1997).
*e.* Simulancin 3299 which is produced by *S. simulans* 3299, associated with bovine mastitis in Brazil (Nascimento et al., 2005).

2. **Staphylococcins produced by Coagulase- positive Staphylococci**: Some of the bacteriocins produced by Staphylococci are class II bacteriocins which are heat stable and unmodified peptides. Most of these bacteriocins are synthesized with an N-terminal leader sequence which is removed upon secretion (Nes et al., 1996).

**Partially characterized bacteriocins:**

a. Staphylococcin 188 which was isolated from *S. aureus* AB 188, a clinical isolate from wound (Saeed et al., 2004).
b. Bac201 is a bacteriocin-like inhibiting substance produced by *S. aureus* AB201, a clinical strain isolated from wounds (Iqbal et al., 1999).
c. Staphylococcin Au-26 which is produced by vaginal *S. aureus* strain (Scott et al., 1992).
d. Staphylococcin 414 is one of the staphylococcin which has a broad spectrum of activity (Gagliano et al., 1970).
e. Staphylococcin IYS2 is the staphylococcin produced by *S. aureus* strain IYS2 isolated from human saliva (Nakamura et al., 1983).

**Fully characterised bacteriocins:**

a. Aureocin A70 is a class II bacteriocin which is produced by *S. aureus* A70. isolated from commercial milk (Giambiagi et al., 1990).
b. Aureocin A53 is also a class II bacteriocin produced by *S. aureus* A53 isolated from commercial milk (Giambiagi et al., 1990).

Other bacteriocins include the class III bacteriocin Lysostaphin which is produced by *S. simulans biovar* staphylolyticus ATCC1362 (Schindler et al., 1964).

## STAPHYLOCOCCINS AGAINST BOVINE MASTITIS:

Milk and dairy products are the important part of a healthy diet, but if consumed unpasteurized they can also represent a health hazard due to the possible contamination by pathogenic bacteria, studied by CDC in Feb. 2012 (Langer et al., 2012). Bovine mastitis is the disease which is most prevalent in dairy cattle worldwide and has a significant impact on milk quality (Lejeune and Rajala-Schultz, 2009). This disease results in significant financial costs to the dairy industry due to decreased milk production and quality (Bradley, 2002; Huijps, Lams and Hogeveen, 2008).

Several bacterial pathogens can cause mastitis, *Staphylococcus aureus* is generally the most important among the etiologic agents present in mastitis in cattle (Anand Kumar, 2009;

Olde Riekerink et al., 2008; Piccinini et al., 2010). *S. aureus* is the most infectious because it causes a chronic and deep infection in mammary glands that is extremely difficult to eradicate (Brouillette and Malouin, 2005). Traditional strategies used against this disease are vaccination and antibiotic treatment. However, the increased use of antibiotics can contribute to the emergence of antibiotic resistant varieties which can be transmitted to the consumers by milk (Brito and Lange, 2005; Sawant, Sordillo and Jayarao, 2005). Thus the need for alternative methods started the use of bacteriocins. Staphylococcins are the bacteriocins produced by staphylococci and the staphylococcins epidermin and aureocin A53 produced by *S.epidermis* and *S. aureus* strains have activity against bovine mastitis ( Augustin et al., 1992; Sandiford and Upton, 2012). According to patent WO1995005844A1 PCT dipping the teat or intramammary injection with Gallidermin and/or Epidermin or one of their pharmaceutically acceptable acid salts. These can be administered prior to the infection to effectively suppress the rate of infection, severity and duration of subsequent bacterial infection or can also be administered to treat mastitis.

## HIGHLY AGGLUTINATIVE STAPHYLOCOCCIN IN CANCER TREATMENT:

Staphylococcal enterotoxin (SE) is a protein which has high biological activity with a superantigen (Sag). It is a bacterial exotoxin which has strong stimulating capability and a variety of immunological activities. SE stimulates a large number of T lymphocytes, promoting differentiation into viable cytotoxic T- cells, promoting the secretion of cytokines ( leukocyte interleukin-2, interferon, tumour necrosis factor, colony stimulating factor) and activating monocytes of NK cells (Dohlsten et al., 1993; D'orazio et al., 1995).

Highly agglutinative staphylococcin (HAS) are derived from the *Staphylococcus aureus* metabolite superantigen. Highly agglutinative staphylococcin (HAS) inhibits and kills tumours, repairs tissues and cells, elevates white blood cell count and improves the immune function. It is a biological bacterial response modifier which is efficient, has low toxicity and a significant enhancing effect on immunity (Andersson et al., 1989; Chen, 2005). The immunological effect of highly agglutinative staphylococcin acts by activating T-cells and natural killer cells, enhancing phagocytes' phagocytosis and destroying lymphocytes, increasing white blood cell count in peripheral blood, repairing impaired histiocytes as well as directly inhibiting the growth of tumour cells (Gan et al., 2000). Researchers have treated the advanced gastrointestinal tumours with Highly agglutinative staphylococcin (HAS) in combination with chemotherapy in the clinical studies and the results showed that the tolerance of the patients to chemotherapy was increased and Highly agglutinative staphylococcin (HAS) can effectively increase and maintain white blood cell count, improve neutrophil levels and prevents bone marrow suppression induced by the chemotherapy (Chen, 2001).

## STAPHYLOCOCCINS AS FOOD BIOPRESERVATIVE:

The competitive activity of bacteria for occupying the same ecological niche and their antagonistic activity can be exploited for their application in food preservation (Cotter et al., 2005; Cleveland et al., 2001). There is demand for safe foods with long shelf life which do not

contain the chemical preservative. Bacteriocins possess potential potential biotechnological application as food preservative as they are effective against key pathogens in food borne illness including Listeria monocytogenes which is an important pathogenic bacteria present in environment and difficult to control in foods (Galvez et al., 2007). Staphylococcin Aureocin A70 and A53, both produced by *S. aureus* are bacteriocins that exhibit antilisterial activity (Netz et al., 2001). These leaderless bacteriocins have been demonstrated to have no cytotoxic and hemolytic activities, thus their application is regarded as safe (Fagundes et al., 2016a,b). Another staphylococcin is warnericin RB4, a lantibiotic is capable of inhibiting the growth of *Alicyclobacillus acidoterrestris,* thermoacidophilic spore former that has been recognized as a food spoilage microorganism (Minamikawa et al., 2005; Cerny et al., 1984; Mclntyre et al., 1995). *A. acidoterrestris* is considered one of the most important target organisms in quality control of fruit juices and fruit juice containing beverages, because of its ability to germinate and outgrow spores under highly acidic conditions (yamazaki et al., 1996; Baumgart et al., 1997).

## USE OF STAPHYLOCOCCIN IN SKIN INFECTIONS:

The most prevalent organism in skin infections are *Staphylococcus aureus* and methicillin resistant *S. aureus* (MRSA) and have become a serious problem in hospitals (Guggenheim et al., 2009; Lesseval and hadjiiski 1996., Taylor et al., 1992). Epidermin and gallidermin produced by *Staphylococcus epidermidis* and *Staphylococcus gallinarum* proved effective in the treatment of skin infections (Kellner et al., 1988). these staphylococcins are also effective against *P. acnes* (Jung, 1991a; Kellner et al., 1988; Niu and Neu 1991). treatment with gallidermin results in the potassium release from the *Staphylococcus simulans* and *Micrococcus flavus* (Bonelli et al., 2006). Gallidermin and epidermin are also effective against eczema, folliculitis and acne and thus, might be used for personal care products (Ryan et al., 2002).

## ANTIFUNGAL ACTIVITY OF STAPHYLOCOCCIN:

Yeast *Candida albicans* is a virulent strain which is naturally present in every body, usually in mucous membrane such as inside of the mouth , on moist skin , vagina, intestines, on and under fingers and toenails (Oscar et al., 2000).some conditions when this yeast overgrow includes thrush, vaginal yeast infections and even diaper rash (Debbie et al., 2004).Candidiasis caused by Candida infection is mainly treated by application of azole derivatives, polyenes, fluoropyrimidines which interfere with the biosynthesis of ergosterol in the fungal cell membrane (Tserkovniak et al., 2009). The yeast can multiply rapidly, penetrate the intestinal lining and move into the bloodstream whenever the immune system is weak. The yeast population is controlled by probiotic or bacteriocin from bacteria (Cheryl et al., 2001; Boonnaert et al., 2000). Staphylococcin Bac188 showed very potent activity against many clinical isolates and is active against many gram positive but not gram negative bacteria and also has activity against candida infections (Hena and Sudha, 2011).

## IN NOSOCOMIAL INFECTIONS:

Some strains originated outside the hospitals having moved into the hospitals which are mainly MRSA strains resistant to methicillin antibiotic (Chaudhary et al., 2017). MRSA has gradually disseminated and is now a major problem in hospitals and is increasingly recovered from nursing homes. Coagulase negative staphylococci, such as *S. epidermis, S. haemolyticus* and *S. saprophyticus* can also be found in association with human infections. These are the most frequently reported pathogens in nosocomial infections worldwide (Rupp and Archer., 1994; Casey et al., 2007). Increasing antibiotic resistance results in the use of the bacteriocins against these strains. Staphylococcin Bac 188 showed potent activity against these strains and also against *Mycobacterium tuberculosis* (Hayek and Ibrahim, 2013).

## ROLE OF STAPHYLOCOCCIN AGAINST BIOFILM PRODUCTION:

The increasing use of indwelling intravascular catheters for diagnostics of diseases has led to the increase in the number of medical device related infections (Casey et al., 2007). This could result in sepsis in patients (Vuong and Otto, 2002; Sader et al., 2003). Lysostaphin, a class III staphylococcin, was tested as a preventive agent in surface colonization by either *S. aureus or S. epidermidis*. Lysostaphin disrupts the extracellular matrix of *S. aureus* films *in vitro* on plastic and glass surfaces (Wu et al., 2003). Lysostaphin was tested on different surfaces and then were infected by infectious strains. The lysostaphin coated catheters were completely cleared of bacteria as compared to the control catheters (Shah et al., 2004). Pep5 and epidermin were also able to cause a significant reduction (90%) of the bacteria adhesion to silicone catheters. These two staphylococcins have also inhibitory activity against *Corynebacterium spp.* cells (Fontana et al., 2006).

## STAPHYLOCOCCINS IN ORAL CARE:

Staphylococcin IYS2 presented an inhibitory spectrum which included typical oral indigenous bacteria, *Streptococcus salivarius, Propionibacterium acnes, actinomycetes israelii strains* (Nakamura et al., 1983). *A. israelii* is the strain which colonizes the dental plaque and may enter into the bloodstream by accident during dental work resulting in actinomycosis disease. This disease is characterized by the formation of painful abscesses in the mouth, lungs or digestive organs and in severe cases these abscesses grow larger and may penetrate the muscles and bone (Bowden, 1996). Use of staphylococcin IYS2 in buccal cavity or in toothpaste could help to reduce the population of these bacteria in mouth, preventing the formation of dental plaque and cavities and thus reducing the risk of actinomycosis development (Bowden et al., 1996).

## CONCLUSION:

Staphylococcus have presented itself as potent inhibitors of hard to kill microorganisms like MRSA and merit their usage in management of higher order infections prevalent in hospital settings both as treatment regimen and Hygiene management protocols. More studies should be

initiated to look into various novel applications of Highly agglutinative staphylococcin (HAS) in fields like activity profile cancer treatment, Biopreservatives, Fungicidal, Oral hygiene and other infections in humans and animals.

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