



International Journal of Medical and All Body Health Research

Virulence factors and protein secreted by *S. aureus* to protect itself from the host's immune system

Takele Worku ^{1*}, Ebisa Mezgebu ², Abdallah Bulbula ³

¹⁻³ Animal Health Institute, Sebeta, Ethiopia

* Corresponding Author: **Takele Worku**

Article Info

ISSN (online): 2582-8940

Volume: 04

Issue: 03

July-September 2023

Received: 15-07-2023;

Accepted: 10-08-2023

Page No: 27-33

Abstract

The most harmful of the numerous common staphylococcal bacteria is *Staphylococcus aureus*, a gram-positive organism that causes a wide range of clinical diseases, including skin infections, bacteremia, endocarditis, pneumonia, and food poisoning. A variety of *S. aureus* virulence factors help to establish infection by encouraging tissue attachment, tissue invasion, and invasion of the host immune response. *S. aureus* is a pathogenic bacteria that, although being a commensal in both humans and animals, has the ability to produce several toxic and enzymes that allow it to penetrate the host body and cause a variety of infections, some of which may be regarded as life-threatening diseases. Virulence factors provide mechanisms for bacterial growth support and disease-causing processes. Numerous virulence traits that *S. aureus* possesses enable it to success as a pathogen. Additionally through the secretion of proteins, *S. aureus* can activate host zymogens, which in turn can target certain defense components. Secreted proteins can also prevent neutrophils or the complement system's proteases from destroying pathogens, which raises the possibility that *S. aureus* will survive. The review aims to highlight *S. aureus* virulence factors and secretion protein that help the bacteria to survive from host immune system.

Keywords: Virulence factors, staphylococcus aureus, immune evasions, s. aureus secretion proteins

1. Introduction

Gram-positive bacteria called *Staphylococcus aureus* is the most dangerous of all of the many common staphylococcal bacteria and responsible for a large number of clinical illnesses including skin infections, bacteremia, endocarditis, pneumonia, and food poisoning. A number of virulence factors expressed by *S. aureus* aid in the establishment of infection by promoting tissue attachment, tissue invasion, and invade the host immune response ^[11]. Besides being equipped with a range of virulence factors and toxins that cause numerous diseases, *S. aureus* has numerous antimicrobial resistance mechanisms and can form a structure known as a biofilm ^[38, 5]. The biofilm is a three-dimensional community of micro-organisms incorporated in an extracellular polymeric substance (EPS), in which the EPS is composed of polysaccharides, proteins and extracellular DNA. This sessile bacterial community can decrease antibacterial and antimicrobial action and increase protection against host defense mechanisms. *S. aureus* is a major cause of hospital-acquired and community-acquired infections, having a significant impact on human and animal health ^[21].

The increasing burden of antimicrobial resistance in *S. aureus* and other staphylococci causing skin infections in companion animals is worrisome as it limits the available therapeutic options for the management of these infections, with a direct impact on animal morbidity and mortality. In the last decades, growing evidence suggests that close contact with humans is a source of transfer of *S. aureus* strains from humans to animals and vice-versa which also provides for the possible movement of antimicrobial resistance determinants between hosts ^[37]. This evidence, together with the increasing presence of companion animals in human households, has led to the consideration of animal-associated Methicillin-resistant *Staphylococcus aureus* (MRSA) strains as a public health risk ^[11].

This review aims to provide an updated literature overview on, virulence, and secretion protein of *S. aureus* as well as the mechanisms by which these secretion proteins interact with the host immune system.

2. Virulence factors of *Staphylococcus aureus*

After the germs have successfully infiltrated the host tissues and gotten past the immune system's protective barriers to enter the bloodstream, *S. aureus* infections occur when the mucosal or epidermal barriers are breached. *S. aureus* and its arsenal of virulence factors are responsible for a wide range of infections and diseases in both humans and animals. These components can also shield *S. aureus* from the human immune system's recognition and reaction [26]. Antigens, enzymes, and toxins are among *Staphylococcus aureus*' Virulence factors components.

2.1. Antigens

2.1.1. Capsule

S. aureus capsular antigens are surface associated, limited in antigenic specificity, and highly conserved among clinical isolates [32]. The capsule enhances staphylococcal virulence by impeding phagocytosis, resulting in bacterial persistence in the bloodstream of infected hosts. Although the capsule has been shown to modulate *S. aureus* adherence to endothelial surfaces in vitro, animal studies suggest that it also promotes bacterial colonization and persistence on mucosal surfaces. Similar to other bacterial pathogens, *S. aureus* expresses capsular polysaccharides (CP) as virulence factors that can protect the pathogen from complement binding and subsequent phagocytic killing by neutrophils [29]. There are two major capsular polysaccharide types, CP5 and CP8 and all clinical *S. aureus* strains have the biosynthetic pathways for making either CP5 or CP8 [30].

2.1.2. Adhesins

In order to start an infection, *Staphylococcus aureus* can colonize the host via attaching to extracellular matrix elements. *S. aureus* is equipped with a diverse array of adhesion mechanisms that enable it to elude host immunity. Adherence is mediated by surface protein adhesins. These adhesins are essential for infection, particularly in the initial stages of attachment when the cells are under physical strain [8].

2.2. Enzymes

2.2.1. Coagulase

Coagulase (coa) is a "historic" *S. aureus* protein that is best known for its ability to induce blood coagulation, which enables the classification of the staphylococcal genus into coagulase-positive or -negative species. More recent studies have shown that *Coa* is a critical Virulence factor in staphylococcal diseases [19]. *S. aureus* secretes two proteins that promote coagulation, coagulase (*Coa*) and von Willebrand factor binding protein (vWbp) that bind to and activate prothrombin, thereby converting fibrinogen to fibrin and promoting the clotting of plasma or blood [28]. The ability to coagulate the plasma is a first step in the diagnosis of these bacteria, as *Coa* and vWbp secretion is among key virulence strategies enabling staphylococci to overcome the host defense system. Nonenzymatic activation of prothrombin coagulases triggers the polymerization of fibrin, resulting in cross-linking of bacteria in the clot, which in turn allows the bacteria to escape from the bactericidal activity of the host

immune system. Development of additional vWbp increases coagulation kinetics of particular host plasma, indicating not only host-preference of staphylococcal strains, but also the importance of coagulases in virulence of these bacteria [4]. Paradoxically, *S. aureus* apply coagulases to induce plasma clotting, which in turn allows the bacteria to escape from the bactericidal activity of the host immune system. Thus, coagulases are among key virulence strategies promoting abscess pathogenesis, and infection persistence, as well as sepsis and endocarditis [28].

2.2.2. Hyaluronidase

Hyaluronidases are bacterial enzymes that cleave the β -1,4 glycosidic bond of hyaluronic acid, a main component of the mammalian extracellular matrix [13, 16]. Hyaluronic acid is synthesized and secreted from the plasma membrane of mammalian cells, and it is abundant in the skin, skeletal tissue, umbilical cord, lungs, heart valves, brain, and a number of other tissues. Hyaluronic acid also performs a multitude of functions for the host, including providing structure to tissues and water homeostasis, assisting with cell proliferation, and acting as an immune regulator. Hyaluronidases are thought to act as spreading factors, allowing dissemination of pathogens throughout mammalian tissue during infection [15]. *S. aureus* is organisms capable of producing hyaluronidase to cause infections initiated at a mucosal or skin surface of either humans or animals [40].

2.2.3. Staphylokinase (invasin)

Staphylokinase (SAK; also known as staphylococcal fibrinolysin) is a protein produced by *Staphylococcus aureus*. It contains 136 amino acid residues and has a molecular mass of 15kDa. Synthesis of staphylokinase occurs in late exponential phase [3]. It is a plasminogen activator secreted by the majority of *S. aureus* strains. It forms complexes with trace amounts of plasmin present in host plasma. Those complexes subsequently cleave plasminogen to form active plasmin, a potent broad spectrum protease targeting host proteins, including fibrin clots. Plasminogen activation by SAK promotes bacterial entry and further spread in the skin [22]. It plays an important role in virulence by facilitating clot disintegration and dissemination of bacteria in host tissues. SAK also contributes to virulence by reducing opsonic activity [10].

2.2.5. Lipases

S. aureus lipase (SAL), which belongs to the glycerol ester hydrolases, shows strong cytopathicity to host cells. SAL is one of the etiological factors of *S. aureus* and it interferes with granulocyte function in the host and increases the survival of the bacterium during host defense by inactivating germicidal lipids [14]. In addition, when it is attached to the skin *S. aureus* strongly reduces the barrier function of the skin using SAL. It contributes to skin colonization by hydrolyzing human sebum as a nutrient source. It has been observed that lipase activity is associated with cell necrosis toxicity. SAL also contributes to colonization and invasion by *S. aureus*. It hydrolyzes lipids, making it possible for the bacteria to survive in sebaceous areas of the body [42].

2.2.6. Penicillinase

Penicillinase is an extracellular enzyme that exits the bacterial cell to break down penicillin nearby by hydrolyzing

the cyclic amide link in the beta-lactam ring of the antibiotic and rendering it inactive, may arise in a bacterial strain exposed to penicillin [41]. *S. aureus* is one of bacteria which produce penicillinase to hydrolyze the penicillin β -lactam ring, leading to resistance to penicillin.

2.2.7. Catalase

Staphylococcus aureus is a gram positive, catalase and coagulase positive coccus and by far the most important pathogen among the staphylococci. It produces enzymes such as catalase which are considered to be virulence determinants [7]. This enzyme breaks down hydrogen peroxide to water and oxygen, and this enzyme could serve to protect ingested staphylococci from the lethal effects of hydrogen peroxide produced by polymorphonuclear neutrophils and **enhances ability to *Staphylococcus aureus* withstand hydrogen peroxide's ability to destroy intra- and extracellular bacteria** [27].

2.3. Toxins

2.3.1 Hemolysins (α , β , γ)

Hemolysins are toxins that lyse red blood cells and their action is usually receptor-mediated. There are many classes of hemolysins, including α , β and γ -hemolysins. δ -hemolysin has been classified as a phenol-soluble modulins (PSM) that does not require a receptor for its hemolytic activity. α -hemolysin is the most well studied member of staphylococcal hemolysins. This small β -barrel pore-forming cytotoxin lyses red blood cells and leukocytes, but not neutrophils [11], via binding to its proteinaceous receptor ADAM10, a disintegrin and metalloproteinase [45]. Upon binding of the toxin with its receptor, pore formation on cell membranes will cause Ca^{2+} influx and K^{+} efflux; this disruption in homeostasis, in turn, leads to necrotic cell death. β -hemolysin is non-pore-forming and has been characterized as a sphingomyelinase. The toxin hydrolyses sphingomyelin and also lyses monocytes; however, it only lyses erythrocytes at low temperatures and is not cytolytic to lymphocytes and granulocytes [44]. γ -hemolysin is hemolytic to rabbit erythrocytes and its membrane damaging activity is also apparent in leukocytes (neutrophils, monocytes, granulocytes, and macrophages) [43].

2.3.2. Leukocidin

The *Staphylococcus aureus* leukotoxin ED (LukED) is a pore-forming toxin required for the lethality associated with bacteremia in murine models. LukED targets the chemokine receptor CCR5 to kill T lymphocytes, macrophages and dendritic cells [36]. The two protein subunits of each leukotoxin are classified as 'S' and 'F'. This nomenclature corresponds to the initial purification of Panton-Valentine leukocidin (PVL) where the first eluted subunit was termed fast (F), and the subunit that eluted subsequently was termed slow (S) [46]. In animal models, LukS-PV and LukF-PV bind to TLR2 and TLR4 whilst, in humans, the receptor for LukED is CCR5, whereas the receptors for PVL and LukAG/GH are C5aR, C5L2, and CD11b, respectively [20].

2.3.3. Enterotoxin

Staphylococcal enterotoxins (SEs) are produced by some *Staphylococcus aureus* strains contaminating foodstuffs and are the real causative agents of staphylococcal food poisoning [24]. Staphylococcal enterotoxins (SEs) belong to a large family of staphylococcal

and streptococcal pyrogenic exotoxins (PT), sharing common phylogenetic relationships, structure, function, and sequence homology. These toxins cause toxic shock-like syndromes and have been implicated in food poisoning and several allergic and autoimmune diseases. Included within this group are the staphylococcal enterotoxins, two forms of toxic shock syndrome toxin (TSST), and a group of streptococci pyrogenic exotoxins [2, 33]. The *S. aureus* enterotoxins (SEs) are potent gastrointestinal exotoxins synthesized by *S. aureus* throughout the logarithmic phase of growth or during the transition from the exponential to the stationary phase. They are active in high nanogram to low microgram quantities, and are resistant to conditions (heat treatment, low pH) that easily destroy the bacteria that produce them, and to proteolytic enzymes, hence retaining their activity in the digestive tract after ingestion [1].

2.3.4. Exfoliative toxin

Exfoliative toxins (ETs) are secreted virulence factors produced by staphylococci. Exfoliative toxins (ET), also known as epidermolytic toxins, are exotoxins produced by strains of *S. aureus* in the epidermis of the host cell, causing loss of keratinocytes, skin exfoliation and blistering [17]. Exfoliative toxin (ET) selectively digests one of the intracellular adhesion molecules, desmoglein 1, of epidermal keratinocytes and causes blisters due to intraepidermal cell-cell dissociation [25].

2.3.5. Toxic shock syndrome toxin

A rare consequence of infection with *Staphylococcus aureus*, specifically toxin-producing strains, is staphylococcal toxic shock syndrome (TSS). Although the triggering infection may seem modest, toxins—TSS toxin-1 (TSST-1) being the most frequently mentioned—act as superantigens, inducing an excessively ecstasitic immune response and cytokine avalanche [39]. *Staphylococcus aureus* is a significant cause of mastitis in dairy cows throughout the world. The bovine mammary gland can be a significant source of enterotoxigenic strains of *S. aureus*. Enterotoxins produced by enterotoxigenic strains of this organism are classified according to serotypes into A–H groups and the presence of the so-called 'toxic shock syndrome toxin' (TSST). TSST was detected in *S. aureus* strains in milk from cows with clinical and subclinical mastitis and also from farm bulk tank milk. Various other studies also implicated bulk tank milk as a potential source of enterotoxigenic *S. aureus* in milk and milk products. Consumption of raw milk generally increases the chances of direct contact with food pathogens such as *S. aureus* and its toxins [18].

3. Proteins produced by *S. aureus* that aid in host immune evasion

In addition to having heightened antibiotic resistance, the *S. aureus* is a master at adjusting to its host by dodging nearly every aspect of the immune system, known as immune evasion proteins. The majority of these immune evasion proteins specifically target neutrophils, which are crucial for eradicating *S. aureus* infections [6].

3.1. Chemotaxis inhibitory protein of *S. aureus* (CHIPS)

The bacterial pathogen *Staphylococcus aureus* is insensitive to antimicrobial host defense peptides such as defensins, protegrins, platelet microbicidal proteins and bacteriocins. Staphylococci have developed various resistance

mechanisms including those specific for bacteriocins and several host defense peptides [35]. A protein belonging to the resistance mechanism of *Staphylococcus aureus* is known as CHIPS (Chemotaxis Inhibiting Protein of *Staphylococcus aureus*). CHIPS is a protein produced by *Staphylococcus aureus* that inhibits chemotaxis of neutrophils by blocking the Formyl Peptide Receptor (FPR) and C5a Receptor on neutrophils. CHIPS and antibodies against CHIPS can be useful for various experimental infection models of *Staphylococcus aureus*. Chemotaxis inhibitory protein of *Staphylococcus aureus* (CHIPS) is an exoprotein produced by several strains of *S. aureus*, and a potent inhibitor of neutrophil and monocyte chemotaxis toward C5a and formylated peptides like fMLP [42].

3.2. *S. aureus* Complement avoidance mechanisms

The complement system is a proteolytic cascade of plasma proteins, which is crucial to the host's defense against invading bacteria [34]. *S. aureus* developed different mechanisms to avoid the action of the complement system by producing a number of proteins that can change and affect the stages of the complement cascade, these mechanisms include; preventing complement identification; cleavage of complement proteins; and/or inhibit the interaction of complement receptors on phagocytes [26]. Although, the

classical pathway C1 complex has the ability to recognize the microbe bound IgG and IgM antibodies and the lectin pathway (mannose-binding lectins and ficolins) bind the saccharide elements of microbe, *S. aureus* produce two surface proteins that can damage and harm the IgG function (Fig 1), the first protein is the Staphylococcal protein A (SpA) and the second protein is known as the Staphylococcal immunoglobulin binding protein (Sbi). Staphylococcal protein (SpA) is a protein located on the surface of the bacterium that consists of four or five immunoglobulin binding domains. Every domain is able to combine with the Fc parts of IgG antibody, thus inhibiting the interaction with Fc receptors on neutrophils in vitro [6]. Staphylococcal Sbi is made up of four parts of Sbi-I and Sbi-II, which can also bind to IgG. Sbi has been shown to play specific functions in limiting Fc-receptor-mediated phagocytosis as well as reducing the binding of C1q and the subsequent activation of the complement classical pathway [18]. *S. aureus* also uses a different technique to avoid being detected by the complement system, removing and destroying the opsonic molecules from its surface using a proteolytic process. Opsonic molecules, like the C3b component of the complement system, are those that can bind to both an antigen and the receptors of phagocytic cells [23].

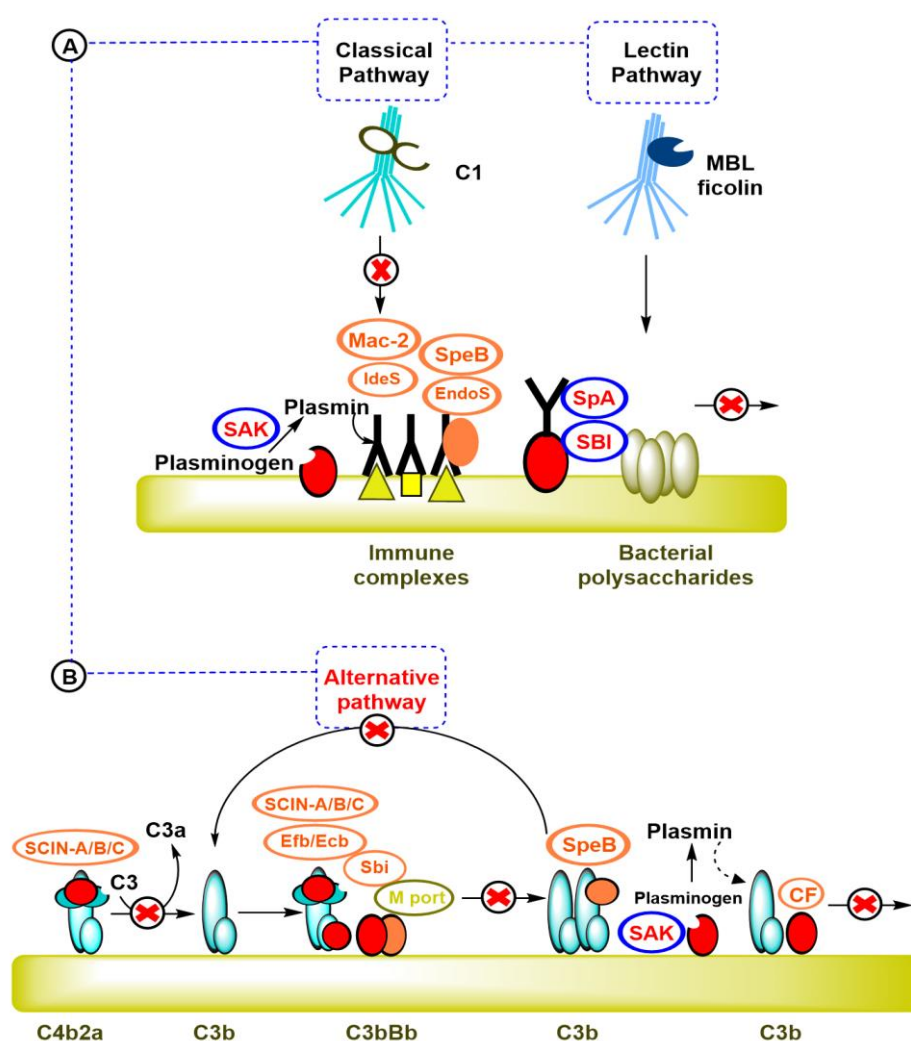


Fig 1: *Staphylococcus* evasion of complement recognition: (A)- *S. aureus* produce two surface proteins that can damage and harm IgG function; Staphylococcal protein A (SpA) and Staphylococcal immunoglobulin binding protein (Sbi). (B)- Presence of the C3 convertases is significant for the activation of complement system and for the response of host immune cells. *S. aureus* use three ways to affect and change this vital step in the complement cascade [26].

3.2. Extracellular fibrinogen binding protein (Efb)

Staphylococcus aureus secretes extracellular fibrinogen-binding protein (Efb) into the cytoplasm of macrophages to suppress host immunity [47], delay wound healing in a rat wound infection model and inhibit neutrophil adherence to immobilized fibrinogen. Efb protein has a disordered N-terminal fibrinogen-binding region and a folded C3-binding domain in the C-terminal region. Efb acts as an allosteric inhibitor by inducing conformational changes in factor C3b that propagate across several domains and influence functional regions far removed from the Efb binding site [34].

3.3. Staphylokinase (SAK)

Staphylokinase (Sak) is a plasminogen activator protein that is secreted by many *Staphylococcus aureus* strains [31]. SAK is structurally most similar to CHIPS and contains a β -grasp-like fold. SAK is a plasminogen activator and is not an enzyme by itself, but forms a complex with human plasminogen, a potent serine protease, and activates it to cleave fibrin and extracellular matrix proteins. Additionally, at the bacterial surface, it activates plasminogen to cleave bound IgG and C3b, thereby indirectly blocking opsonization and complement activation, which consequently interferes with neutrophil phagocytosis. SAK also directly binds to human α -defensin and inhibits its antimicrobial potency [48].

3.4. Extracellular adherence protein (Eap)

The extracellular adherence protein (Eap) of *Staphylococcus aureus* is a secreted protein known to exert a number of adhesive and immunomodulatory properties. Secreted Eap has been shown to interact with a number of host cell matrix components, plasma proteins, and cellular receptors with a binding preference for extracellular cell matrix (ECM) superstructures. Eap demonstrated function as a potent anti-inflammatory and anti-angiogenic factor. This multifunctional protein is also involved in biofilm formation under iron-limiting conditions or in the presence of serum [9]. Extracellular adherence protein (Eap) is a virulence factor expressed by the vast majority of *S. aureus* strains and consists of four to six repeats. Eap has many functions, including involvement in adherence and internalization of the bacteria into eukaryotic cells and anti-inflammatory activities mediated through binding to intercellular adhesion molecule type 1 (ICAM-1), resulting in impairment of neutrophil and T-cell recruitment. Eap has also been shown to inhibit T-cell responses [12].

4. Conclusion

Staphylococcus aureus is Gram-positive bacteria that can cause a variety of broad spectrum of diseases, from simple skin and soft tissue infections to major bloodstream infections that can be fatal. *S. aureus*' detrimental lifestyle is supported by a variety of virulence factors, such as toxins, enzyme, antigen, and immune-modulating compounds. The handling of host proteins involved in the complement system, coagulation cascade, and fibrinolysis cascade is a specialty of *Staphylococcus aureus*. Proteins involved in these processes move through bodily fluids or exist as inactive zymogen in the extracellular matrix, where they can become active by interacting with certain secreted staphylococcal proteins. In contrast, *S. aureus* secretes particular proteinaceous inhibitors of host serine proteases that are vital to immunological response.

Declarations

Ethical approval

Not applicable

Availability of data

Not applicable

Competing of interest

The author declares that there is no competing of interest regarding the publication of the manuscript.

Funding

Not applicable

Author contribution

TW wrote the first manuscript draft. EM read the manuscript and revised it critically before approving the final, submitted version.

5. References

1. Argudín MÁ, Mendoza MC, Rodicio MR. Food poisoning and *Staphylococcus aureus* enterotoxins. *Toxins*. 2010; 2(7):1751-1773.
2. Balaban N, Rasooly A. Staphylococcal enterotoxins. *International journal of food microbiology*. 2000; 61(1):1-10.
3. Bokarewa MI, Jin T, Tarkowski A. *Staphylococcus aureus*: staphylokinase. *The international journal of biochemistry & cell biology*. 2006; 38(4):504-509.
4. Bonar E, Międzobrodzki J, Władyka B. The staphylococcal coagulases. In *Pet-To-Man Travelling Staphylococci*, 2018, 95-102.
5. Costa SS, Ribeiro R, Serrano M, Oliveira K, Ferreira C, Leal M, *et al.* *Staphylococcus aureus* causing skin and soft tissue infections in companion animals: Antimicrobial resistance profiles and clonal lineages. *Antibiotics*. 2022; 11(5):599.
6. De Jong NW, Van Kessel KP, Van Strijp JA. Immune evasion by *Staphylococcus aureus*. *Microbiology spectrum*. 2019; 7(2):7-2.
7. Dezfulian A, Salehian MT, Amini V, Dabiri H, Azimirad M, Aslani MM, *et al.* Catalase-negative *Staphylococcus aureus* isolated from a diabetic foot ulcer. *Iranian Journal of Microbiology*. 2010; 2(3):165.
8. Dufrêne YF, Viljoen A. Binding strength of Gram-positive bacterial adhesins. *Frontiers in microbiology*. 2020; 11:1457.
9. Eisenbeis J, Saffarzadeh M, Peisker H, Jung P, Thewes N, Preissner KT, *et al.* The *Staphylococcus aureus* extracellular adherence protein Eap is a DNA binding protein capable of blocking neutrophil extracellular trap formation. *Frontiers in cellular and infection microbiology*. 2018; 8:235.
10. Francis D, Bhairaddy A, Joy A, Hari GV, Francis A. Secretory proteins in the orchestration of microbial virulence: The curious case of *Staphylococcus aureus*. *Adv. Protein Chem. Struct. Biol.* 2023; 133:271-350.
11. Gnanamani A, Hariharan P, Paul-Satyaseela M. *Staphylococcus aureus*: Overview of bacteriology, clinical diseases, epidemiology, antibiotic resistance and therapeutic approach. *Frontiers in Staphylococcus aureus*. 2017; 4(28):10-5772.
12. Hagggar A, Flock JI, Norrby-Teglund A. Extracellular

- adherence protein (Eap) from *Staphylococcus aureus* does not function as a superantigen. *Clinical microbiology and infection*. 2010; 16(8):1155-1158.
13. Hart ME, Hart MJ, Roop AJ. Genotypic and phenotypic assessment of hyaluronidase among type strains of a select group of staphylococcal species. *International Journal of Microbiology*, 2009.
 14. Hu C, Xiong N, Zhang Y, Rayner S, Chen S. Functional characterization of lipase in the pathogenesis of *Staphylococcus aureus*. *Biochemical and biophysical research communications*. 2012; 419(4):617-620.
 15. Hynes WL, Walton SL. Hyaluronidases of Gram-positive bacteria. *FEMS microbiology letters*. 2000; 183(2):201-207.
 16. Ibberson CB, Jones CL, Singh S, Wise MC, Hart ME, Zurawski DV, *et al.* *Staphylococcus aureus* hyaluronidase is a CodY-regulated virulence factor. *Infection and immunity*. 2014; 82(10):4253-4264.
 17. Ilie MI, Marandiu IM, Velescu BŞ, Udeanu DI, Arsene AL. *Staphylococcus aureus* toxicity, 2023.
 18. Jooste PJ, Anelich L, Motarjemi Y. Safety of food and beverages: milk and dairy products, 2014.
 19. Ko YP, Kang M, Ganesh VK, Ravirajan D, Li B, Höök M. Coagulase and Efb of *Staphylococcus aureus* have a common fibrinogen binding motif. *MBio*. 2016; 7(1):e01885-15.
 20. Kong C, Neoh HM, Nathan S. Targeting *Staphylococcus aureus* toxins: a potential form of anti-virulence therapy. *Toxins*. 2016; 8(3):72.
 21. Kranjec C, Morales Angeles D, Torrissen Mårli M, Fernández L, García P, Kjos M, *et al.* *Staphylococcal* biofilms: Challenges and novel therapeutic perspectives. *Antibiotics*. 2021; 10(2):131.
 22. Kwiecinski J, Peetermans M, Liesenborghs L, Na M, Björnsdottir H, Zhu X, *et al.* *Staphylokinase* control of *Staphylococcus aureus* biofilm formation and detachment through host plasminogen activation. *The Journal of infectious diseases*. 2016; 213(1):139-148.
 23. Laarman A, Milder F, van Strijp J, Rooijackers S. Complement inhibition by gram-positive pathogens: molecular mechanisms and therapeutic implications. *Journal of molecular medicine*. 2010; 88:115-120.
 24. Le Loir Y, Hennekinne JA. Detection of staphylococcal enterotoxins, 2014.
 25. Liu D. Enterotoxin-producing *Staphylococcus aureus*. In *Molecular Medical Microbiology*. Academic Press, 2015, 979-995.
 26. Malak HA, Abulreesh HH, Organji SR, Elbanna K, Shaaban MR, Ahmad I, *et al.* Immune system evasion mechanisms in *Staphylococcus aureus*: current understanding. *J Pure Appl Microbiol*. 2020; 14(4):2219-2234.
 27. Mandell GL. Catalase, superoxide dismutase, and virulence of *Staphylococcus aureus*. In vitro and in vivo studies with emphasis on staphylococcal-leukocyte interaction. *The Journal of clinical investigation*. 1975; 55(3):561-566.
 28. McAdow M, Missiakas DM, Schneewind O. *Staphylococcus aureus* secretes coagulase and von Willebrand factor binding protein to modify the coagulation cascade and establish host infections. *Journal of innate immunity*. 2012; 4(2):141-148.
 29. Mohamed N, Timofeyeva Y, Jamrozy D, Rojas E, Hao L, Silmon de Monerri NC, *et al.* *Molecular epidemiology* and expression of capsular polysaccharides in *Staphylococcus aureus* clinical isolates in the United States. *PloS one*. 2019; 14(1):e0208356.
 30. Nanra JS, Buitrago SM, Crawford S, Ng J, Fink PS, Hawkins J, *et al.* Capsular polysaccharides are an important immune evasion mechanism for *Staphylococcus aureus*. *Human vaccines & immunotherapeutics*. 2013; 9(3), 480-487.
 31. Nguyen LT, Vogel HJ. *Staphylokinase* has distinct modes of interaction with antimicrobial peptides, modulating its plasminogen-activation properties. *Scientific reports*. 2016; 6(1):31817.
 32. O'Riordan K, Lee JC. *Staphylococcus aureus* capsular polysaccharides. *Clinical microbiology reviews*. 2004; 17(1):218-234.
 33. Ortega E, Abriouel H, Lucas R, Gálvez A. Multiple roles of *Staphylococcus aureus* enterotoxins: pathogenicity, superantigenic activity, and correlation to antibiotic resistance. *Toxins*. 2010; 2(8):2117-2131.
 34. Pietrocola G, Nobile G, Rindi S, Speziale P. *Staphylococcus aureus* manipulates innate immunity through own and host-expressed proteases. *Frontiers in cellular and infection microbiology*. 2017; 7:166.
 35. Peschel A, Collins LV. *Staphylococcal* resistance to antimicrobial peptides of mammalian and bacterial origin. *Peptides*. 2001; 22(10):1651-1659.
 36. Reyes-Robles T, Alonzo F, Kozhaya L, Lacy DB, Unutmaz D, Torres VJ. *Staphylococcus aureus* leukotoxin ED targets the chemokine receptors CXCR1 and CXCR2 to kill leukocytes and promote infection. *Cell host & microbe*. 2013; 14(4):453-459.
 37. Schwarz S, Fessler AT, Loncaric I, Wu C, Kadlec K, Wang Yand, *et al.* Antimicrobial resistance among staphylococci of animal origin. *Microbiology spectrum*. 2018; 6(4):6-4.
 38. Silva-de-Jesus AC, Ferrari RG, Panzenhagen P, Conte-Junior CA. *Staphylococcus aureus* biofilm: the role in disseminating antimicrobial resistance over the meat chain. *Microbiology*. 2022; 168(10):001.
 39. Ferguson AJ. *Staphylococcal* toxic shock syndrome: mechanisms and management. *Current infectious disease reports*. 2010; 12:392-400.
 40. Skalka B. Hyaluronidase test in the diagnosis of staphylococci. *Veterinarni Medicina*. 1985; 30(6):373-378.
 41. Soufer D. Protecting penicillin from penicillinase. *Microbios*. 1986; 45(184-185):193-198.
 42. Van Kessel KP, Prossnitz R, van Strijp JA, de Haas CJ. Chemotaxis Inhibitory Protein of. *J Immunol*. 2004; 172:6994-7001.
 43. Vandenesch F, Lina G, Henry T. *Staphylococcus aureus* hemolysins, bi-component leukocidins, and cytolytic peptides: a redundant arsenal of membrane-damaging virulence factors?. *Frontiers in cellular and infection microbiology*. 2012; 2:12.
 44. Walev I, Weller U, Strauch S, Foster T, Bhakdi S. Selective killing of human monocytes and cytokine release provoked by sphingomyelinase (beta-toxin) of *Staphylococcus aureus*. *Infection and immunity*. 1996; 64(8):2974-2979.
 45. Wilke GA, Wardenburg JB. Role of a disintegrin and metalloprotease 10 in *Staphylococcus aureus* α -hemolysin-mediated cellular injury. *Proceedings of the National Academy of Sciences*. 2010; 107(30):13473-

- 13478.
46. Yoong P, Torres VJ. The effects of *Staphylococcus aureus* leukotoxins on the host: cell lysis and beyond. *Current opinion in microbiology*. 2013; 16(1):63-69.
 47. Zhang X, Xiong T, Gao L, Wang Y, Liu L, Tian T, *et al*. Extracellular fibrinogen-binding protein released by intracellular *Staphylococcus aureus* suppresses host immunity by targeting TRAF3. *Nature Communications*. 2022; 13(1):5493.
 48. Kudryashova E, Seveau SM, Kudryashov DS. Targeting and inactivation of bacterial toxins by human defensins. *Biological chemistry*. 2017; 398(10):1069-1085.