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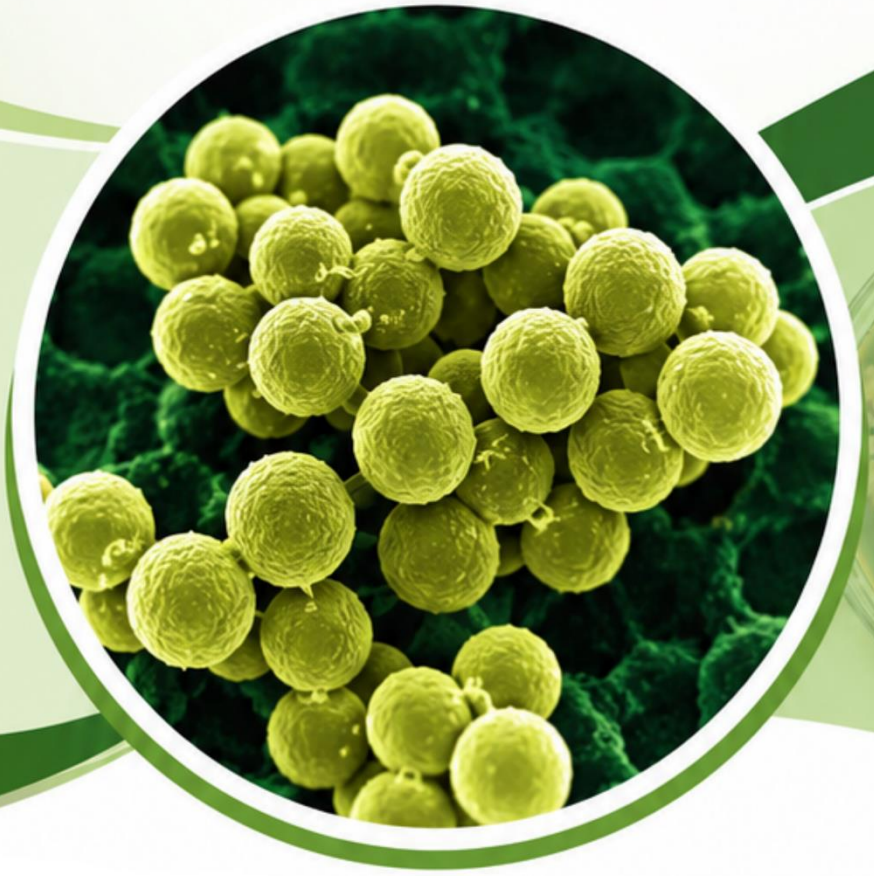

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Staphylococcus aureus: Pathogenesis, Molecular Identification, and Emerging Antibiotic Resistance

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ABSTRACT

Staphylococcus aureus represents one of the most important Gram-positive pathogens known as the cause of different types of infections affecting humans and animals including simple skin infections as well as severe infections like bacteremia, pneumonia, and toxic shock syndrome. Its capabilities related to colonizing host tissues, evading the host immune response, and producing virulence factors make the bacterium highly pathogenic. The increasing number of antibiotic-resistant strains, especially methicillin-resistant *Staphylococcus aureus* (MRSA), presents an enormous problem in public health. This paper presents the main aspects related to the bacterium including the historical background, general features, virulence properties, as well as the infections caused by the organism. Special attention should be paid to the role of molecular techniques in the diagnosis of MRSA and other resistant strains of *Staphylococcus aureus*. Currently, a variety of treatment options are used in medical practice including antibiotics and several other methods which have been recently developed.

KEYWORDS: *Staphylococcus aureus*, virulence factors, antibiotic resistance, mecA gene, nanotechnology, plant-based therapeutics.

1.INTRODUCTION

Staphylococcus aureus is a coccus-shaped, gram-positive bacteria occur in clusters arranged in a grape-like structure which are pathogenic in nature and can cause a large number of diseases. It is found in the skin of mammals and belongs to the staphylococcus genus. It is found on the skin, mucous membranes, the alimentary, and urogenital tracts of various mammals and birds. It has been linked to clinical illness of humans and animals. Among the coagulase-positive Staphylococci, *Staphylococcus aureus* is clinically the most important species in humans. Associated with both community-acquired and hospital-acquired infections, causing mild skin infections to severe diseases, such as bacteremia, pneumonia, toxic shock syndrome, and food poisoning. *Staphylococcus aureus* is a major public health concern worldwide due to its high mortality rates. It leads to bloodstream infections and has a strong ability to adapt to changing environments and spread beyond hospitals into communities [1].

It is not only about illnesses or diseases; it resides in human populations in an asymptomatic manner by making colonies in the nasal passage of a healthy person. This is exactly why it spreads very easily and causes infections and diseases among us. Especially in dairy ruminants and animals, *Staphylococcus aureus* has been recognized as a significant pathogen causing intramammary infection, such as bovine mastitis, which results in a decline in milk production and its quality. These infections can be clinical or subclinical, and transmission occurs through milking, which can spread between animals and humans. The pathogenic potential of *Staphylococcus aureus* is linked to its ability to produce a wide range of virulence factors, including toxins and enzymes that promote tissue invasion, immune evasion, and disease development [2].

The main challenge in controlling *S. aureus* infection is the resistant strain of the *S. aureus*, mainly methicillin-resistant *Staphylococcus aureus* (MRSA). Resistant is due to presence of genetic elements such as mecA gene, which decreases the efficiency of the antibiotic against the bacteria. Apart from this it also has hereditary material like jumping genes and extrachromosomal DNA through which resistance can be gained. It has penicillin-binding protein which reduces the efficacy of β-lactam antibodies. Besides, infection caused by *Staphylococcus aureus*, especially when appear as bacteremia, has potential to cause severe complications such as infective endocarditis, osteomyelitis, septic arthritis, and abscess formation in specimens. Altogether, *Staphylococcus aureus* can spread easily from animals to humans which can make people sick and it is getting difficult day by day to treat it with antibiotics. Which in turn is becoming a big problem so, we need to keep researching and studying about *Staphylococcus aureus* to prevent it from spreading and find a proper treatment for this infection [3].

2. HISTORY

History of *Staphylococcus aureus* is dated back to 19th century, when it was recognized as a human pathogen. Alexander Ogston a Scottish surgeon observed clusters of cocci in pus from surgical abscesses arranged in grape-like structure in 1880, this is how it led to the naming of genus staphylococcus. In 1884, Friedrich Julius Rosenbach a German microbiologist classified species of staphylococcus based on colony pigmentation and named it *Staphylococcus aureus* which appeared in golden-yellow colonies, so it can be differentiated from other species [4].

In 20th century, *S. aureus* was a major cause of wound infections mostly in hospital surroundings. In 1940s a turning point was observed when penicillin was introduced which was seen as a help to manage the *S. aureus* infections, but due to emerges of resistant strains and because of β-lactamase enzymes it was very much clear it was difficult to manage *S. aureus* infections. As the bacteria was penicillin resistant, in a while methicillin was discovered in 1959, but in a short period of time a it was reported as methicillin resistant *Staphylococcus aureus* (MRSA) which was the emergences of major global concern due to antibiotic resistance bacteria. Later on, MRSA became a major concern in healthcare sector as the specimen has the ability to spread rapidly and adapt to its surrounding [5].

Due to advances in molecular biology and genomics improvement in recent years it became easy to study evolution, virulence mechanisms, and antibiotic resistance patterns. In modern studies its genetic flexibility, mobile genetic elements such as mecA gene, and its transmission between humans and animals can be known. Altogether, *Staphylococcus aureus* has been evolved from a simple pathogen to highly adaptable, multidrug resistant organism having a great clinical significance and need continuous study and research [6].

3. GENERAL CHARACTERSITICS OF *Staphylococcus aureus*

S. aureus shows distinct morphological and physiological characteristics that helps the bacteria to survive and helps to make it pathogenic in nature.

Table 1: *Staphylococcus* aureus characteristics.

Feature	Description
Morphology	Gram-positive cocci shaped present in clusters
Size	0.5-1.5µm
Motility	Non-motile
Spore formation	Non-spore
Oxygen requirement	Facultative anaerobe
Habitat	Skin, nasal cavity, mucosa
Colony color	Golden yellow color colonies
Optimum temperature	37ºC
Optimum pH	6-7

Source: Adapted from Fayisa and Tuli (2023) [7].

4. VIRULENCE FACTOR

Staphylococcus aureus is a highly adaptable microorganism, it has numerous factors through which its virulence can be understood i.e., colonization, immune evasion, and tissue destruction. It causes variety of diseases from minor to life-threatening due to virulence factors which allow it cause diseases and are controlled by its complex genetic system [8].

4.1.Adhesion and Colonization Factors

Microbial surface components that recognize adhesive matrix of the host tissue during the initial stage of infection. These protein elements attach to the extracellular matrix of the host, which include keratin, fibronectin, and fibrinogen. Elements such as clumping factors (ClfA and ClfB), fibronectin-binding proteins, and surface proteins (SasG and SasX) are essential to form colony and in the development of infection in nasal cavity and skin [9].

4.2.Biofilm Formation

Formation of biofilm by *S. aureus* plays an important role in colonizing in host tissues and non-living objects like prosthetic devices. Biofilms include of polysaccharides, proteins, and extracellular DNA that act as shield to antibiotic resistance and host defense system. It plays an important role in chronic and reoccurring infections, especially in the environment where infection can spread easily. Biofilm-forming strains have more resistance and persistent than other strains of *S. aureus* [10].

4.3.Toxin Production

It is a pathogenic feature of *S. aureus* contributing to tissue damage and systemic disease.

4.3.1 Cytotoxins

Cytotoxins harm the host cell membranes, like α-hemolysin and phenol-soluble modulins, harm tissues and cause cell lysis [11].

4.3.2 Leukotoxins

It weakens the host defenses and causes serious infections by targeting the immune cells like neutrophils, leukotoxins and Panton-Valentine leucocidin (PVL) [12].

4.3.3 Superantigens

Toxic shock syndrome toxin 1 (TSST-1) and staphylococcal enterotoxins, induce non-specific activation of T cells, leading to cytokines production and in turn leads effects such as toxic [13].

4.4. Immune Evasion Mechanisms

To survive in the host, *S. aureus* adopts a number of immune evasion mechanisms. Through adhering to immunoglobulin G's Fc region, protein A limits phagocytosis and opsonization respectively. Also, the process of complement activation and recruitment of neutrophil are blocked via proteins such as chemotaxis inhibitory protein (CHIPS) and staphylococcal complement inhibitor (SCIN). The formation of capsules act as a shield from phagocytosis. Collectively, these helps in the survival of bacteria following infection [14].

4.5. Enzymatic Virulence Factors

S. aureus has numerous enzymes that aid in tissue invasion and dissemination. Coagulase encourages clot formation which protect the *S. aureus* from the host immune cells, while enzymes such as hyaluronidase, lipases, and proteases break down the host tissue and facilitate spread of germs. Staphylokinase activates plasminogen and break fibrin clots to further dispersion [15].

4.6. Iron Acquisition Systems

Iron intake plays a major role in bacterial development in the host environment. *S. aureus* uses iron-regulated surface determinant (Isd) proteins and siderophores such staphyloferrin A and B to extract hemoglobin from host. These allows the bacteria to boost virulence and survive in iron-restricted environments [16].

4.7. Mobile Genetic Elements and Virulence Diversity

Pathogenicity islands (SaPIs), prophages, and SCCmec elements are some of the mobile genomic elements which encode multiple virulence factors in *S. aureus*. Virulent and antibiotic-resistant strains like MRSA are result of genetic diversity and evolution that facilitate horizontal gene transfer [17].

4.8. Regulation of Virulence Factors

Accessory gene regulator (agr), SarA, and SaeRS are complex regulatory systems which control the expression of virulence factors. The agr system behaves like a quorum sensing regulator that controls the toxin production and virulence gene expression against the population density of bacteria. In turn it helps the bacteria to move from colonization stage to severe infection stage [18].

5. DISEASES CAUSED

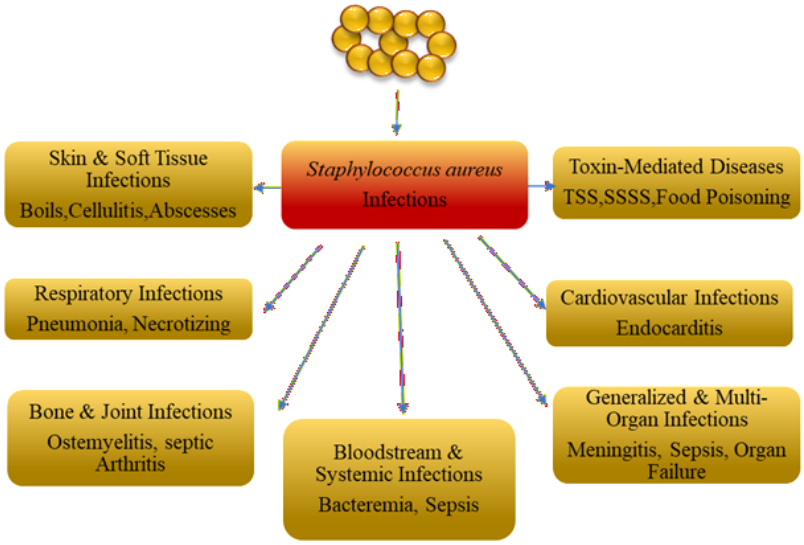

Fig1: *Staphyloccus aureus* Infections.

5.1. Skin and Soft Tissue Infections (SSTIs)

Staphylococcus aureus is the most common etiologic agent responsible for skin and soft tissue infections, which include infections such as boils (furuncles), carbuncles, folliculitis, impetigo, cellulitis, and abscess formation. These infections usually occur when the bacteria penetrate the body through breaches in the skin and result in localized inflammation, pus formation, and tissue destruction. In severe infections, the disease can progress to necrotizing fasciitis, an aggressive and life-threatening condition [19].

5.2. Toxin-Mediated Diseases (Toxinoses)

There are certain strains of *S. aureus* that produce exotoxins, which cause toxin-mediated diseases. These include staphylococcal food poisoning, where pre-formed enterotoxins are ingested, resulting in vomiting and diarrhea. Another condition caused by *S. aureus* is staphylococcal scalded skin syndrome (SSSS), which is characterized by blistering and exfoliation of skin due to the effect of exfoliating toxins. Another condition caused by *S. aureus* is toxic shock syndrome (TSS), which is a severe disease with fever, rash, hypotension, and multi-organ failure due to superantigen toxins like TSST-1 [20].

5.3. Respiratory Tract Infections

Pneumonia and other serious respiratory infections can be brought on by *Staphylococcus aureus*, especially in hospitalized patients or those with compromised immune systems. Complications from staphylococcal pneumonia include necrotizing pneumonia, sepsis, and respiratory failure. High morbidity and fatality rates are linked to the illness, particularly when virulent strains that produce Panton-Valentine leukocidin (PVL) are involved [21].

5.4. Bloodstream and Systemic Infections

Bacteraemia and sepsis, which are linked to significant morbidity and death, can be brought on by invasive infections. *S. aureus* can cause secondary infections and systemic problems after it enters the bloodstream and spreads to several organs [22].

5.5. Cardiovascular Infections (Endocarditis)

Staphylococcus aureus causes infective endocarditis. It involves the colonization of heart valves and the development of vegetation. This may lead to embolism, destruction of heart valves, and heart failure [23].

5.6. Bone and Joint Infections

The bacteria are frequently responsible for septic arthritis and osteomyelitis. Because of the bacterial persistence in tissues and the production of biofilms, these infections are frequently persistent and challenging to cure [24].

5.7. Generalized and Multi-Organ Infections

Meningitis, septicemia, and multi-organ failure are among the widespread infections that *S. aureus* can produce in extreme circumstances. These illnesses frequently pose a threat to life and need for immediate medical attention [25].

6. MOLECULAR IDENTIFICATION OF *Staphylococcus aureus*

Compared to traditional phenotypic approaches, molecular identification of *Staphylococcus aureus* has become a crucial tool in contemporary clinical microbiology because of its high specificity, sensitivity, and quick turnaround time. Even if they are dependable, traditional culture-based methods take a lot of time and might not be able to distinguish closely related species or identify low bacterial loads. Because of its excellent specificity, the nuc gene—which codes for a thermostable nuclease enzyme—is regarded as one of the most trustworthy markers for *S. aureus* identification [26].

Detection of this gene using PCR is widely accepted as a confirmatory method. Methicillin resistance in *S. aureus* is caused by the mecA gene, which also produces a modified penicillin-binding protein (PBP2a) with a low affinity for β-lactam antibiotics [27].

Detection of the mecA gene is critical for identifying methicillin-resistant *Staphylococcus aureus* (MRSA), which is associated with increased morbidity and mortality. For phylogenetic analysis and bacterial identification, the highly conserved 16S rRNA gene is frequently utilized. High sensitivity, specificity, and quick turnaround times are just a few benefits of molecular techniques [28].

Table 1: Molecular Identification of *Staphylococcus aureus* With Primer Usage Strength.

Gene Name	Primer Name	Primer Sequence (5′–3′)	Product Size (bp)	Primer Use Strength	Reference
nuc (thermonuclease)	nuc-F	GCGATTGATGGTGATACGGTT	279 bp	**Strong**	[29]
	nuc-R	AGCCAAGCCTTGACGAACTAAAGC			
mecA (methicillin resistance)	mecA-F	AAAATCGATGGTAAAGGTTGGC	533 bp	**Strong**	[29]

	mecA-R	AGTTCTGCAGTACCGGATTTGC			
mecC (mecA homolog)	mecC-F	GAAAAAAAGGCTTAGAACGCCTC	138 bp	**Moderate**	[30]
	mecC-R	GAAGATCTTTTCCGTTTTCAGC			
16S rRNA	16S-F	AGAGTTTGATCCTGGCTCAG	~1500 bp	**Moderate**	[31]
	16S-R	ACGGCTACCTTGTTACGACTT			
spa (protein A gene)	spa-F	ATCTGGTGGCGTAACACCTG	~200–600 bp	**Moderate**	[32]
	spa-R	CGCTGCACCTAACGCTAATG			
coa (coagulase gene)	coa-F	ATAGAGATGCTGGTACAGG	600–900 bp	**Low**	[33]
	coa-R	GCTTCCGATTGTTCGATGC			

Table 2 : Molecular Identification Methods of *Staphylococcus aureus*.

Method / Technique	**Target Gene / Marker**	**Principle**	**Application**	**Advantages**	**Limitations**	**Reference**
Conventional PCR	nuc gene	Amplification of species-specific DNA sequence	Identification of *S. aureus*	High specificity and sensitivity	Requires thermal cycler; contamination risk	[29]
Conventional PCR	mecA gene	Detection of resistance gene encoding PBP2a	Identification of MRSA	Accurate detection of methicillin resistance	Cannot detect mecC variants in some cases	[30]
16S rRNA Sequencing	16S rRNA gene	Sequencing of conserved bacterial gene	Broad bacterial identification	Universal detection method	Low specificity for closely related species	[31]
Real-Time PCR (qPCR)	nuc, mecA	Fluorescent-based DNA amplification	Rapid clinical diagnosis	Fast, quantitative, highly sensitive	Expensive equipment required	[31]
Multiplex PCR	nuc, mecA, spa	Simultaneous amplification of multiple genes	Detection of virulence and resistance genes	Time-saving and cost-effective	Optimization required	[31]

LAMP	mecA, nuc	Isothermal DNA amplification	Rapid detection in low-resource settings	No thermal cycler needed; quick results	Primer design is complex	[32]
spa Typing	spa gene	Sequencing of polymorphic region of protein A gene	Epidemiological typing	High discriminatory power	Limited use in routine diagnostics	[32]
Whole Genome Sequencing (WGS)	Whole genome	Complete genome sequencing	Outbreak investigation and research	High resolution and detailed analysis	Expensive and time-consuming	[33]

7. ANTIBIOTIC RESISTANCE

A common human pathogen, *Staphylococcus aureus* causes a variety of diseases, such as pneumonia, endocarditis, bacteremia, and infections of the skin and soft tissues. The amazing capacity of the organism to develop resistance to several medicines has made therapeutic therapy of these infections more difficult. Penicillin was initially quite efficient against *S. aureus*, but fast resistance resulted from the widespread synthesis of β-lactamase enzymes. Following the introduction of methicillin as a substitute, methicillin-resistant *Staphylococcus aureus* (MRSA) quickly surfaced. MRSA is currently a major global public health hazard that affects both community (CA-MRSA) and hospital (HA-MRSA) settings [32].

7.1 Mechanism of Antibiotic Resistance

Numerous genetic and metabolic processes contribute to the development of antibiotic resistance in *S. aureus*. Acquisition of the mecA gene, which produces a modified penicillin-binding protein (PBP2a) with a low affinity for β-lactam antibiotics, is one of the most significant processes. This alteration makes β-lactam medications ineffective. Furthermore, *S. aureus* generates β-lactamase enzymes that hydrolyze penicillins' β-lactam ring, rendering the medication inactive. Additional mechanisms include mutations in target locations that decrease drug binding and the existence of efflux pumps that actively remove antibiotics from the bacterial cell [33].

Methicillin – Resistant *Staphylococcus aureus* (MRSA) MRSA strains are challenging to treat because they are resistant to methicillin and other β-lactam medicines. Hospital-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA) are two general categories for these bacteria. While CA-MRSA can infect normally healthy people, HA-MRSA is usually linked to invasive surgeries, extended hospital stays, and immunocompromised patients. Increased morbidity, mortality, and medical expenses are linked to MRSA infections. The advent of vancomycin-intermediate (VISA) and vancomycin-resistant *S. aureus* (VRSA) presents a new therapeutic hurdle, even if drugs like vancomycin, linezolid, and daptomycin are still effective against many MRSA strains [34].

Table 3: Prevention and Control Strategies for Antibiotic Resistance in *Staphylococcus aureus*

Strategy	Description	Key Measures	References
Hand Hygiene	The most basic and successful strategy for stopping the spread of S. aureus in medical environments is hand cleanliness.	Using alcohol-based hand massages both before and after patient contact; routinely washing hands with soap and water .	[35]
Infection Prevention and Control (IPC)	The transmission of resistant strains is limited by standard infection control procedures, especially in hospital settings.	sterilizing tools, using personal protective equipment (PPE), and following aseptic procedures.	[35]
Antimicrobial Stewardship	The emergence and spread of resistance are reduced when antibiotics are used responsibly.	The right choice of antibiotics, the right dosage and duration, and the avoidance of needless prescriptions.	[36]
Rapid Diagnostic Techniques	Early and accurate detection of resistant strains enables timely and targeted therapy.	Implementation of molecular diagnostics such as PCR-based assays and sequencing technologies.	[36]
Screening and Surveillance	Active surveillance helps in early identification and monitoring of MRSA carriers and outbreaks.	Routine screening of high-risk patients, surveillance cultures, and monitoring resistance patterns.	[35]
Environmental Cleaning and Disinfection	Contaminated surfaces and equipment serve as reservoirs for *S. aureus* transmission.	Regular cleaning and disinfection of hospital surfaces and medical devices.	[35]
Patient Isolation and Contact Precautions	Isolation of infected or colonized patients reduces cross-transmission.	Use of dedicated rooms, contact precautions, and cohorting of patients.	[36]
Education and Training	Awareness among healthcare workers and patients improves adherence to prevention strategies.	Training programs on infection control and responsible antibiotic use.	[35]
Development of Novel Therapeutics	New treatment strategies are required to combat	Research on new antibiotics, bacteriophage therapy, and	[36]

	multidrug-resistant *S. aureus*.	alternative antimicrobial approaches.	

8. TREATMENT AND FUTURE RECTIFIERS

8.1. Conventional Antibiotic Remedy

Antibiotic remedy, which varies grounded on the strain's susceptibility profile, is the main treatment for *Staphylococcus aureus* infections. While methicillin-resistant *S. aureus* (MRSA) necessitates alternate drugs like vancomycin, daptomycin, and linezolid, methicillin-sensitive *S. aureus* (MSSA) infections are typically treated with β-lactam antibiotics such nafcillin, oxacillin, and cefazolin. However, therapeutic approaches and clinical results have come considerably more complex due to the rising incidence of antibiotic resistance [37].

8.2. Challenges Due to Antibiotic Resistance

A significant threat to world health is the rise of multidrug-resistant strains like MRSA and vancomycin-intermediate or resistant *S. aureus* (VISA/VRSA). Target site modification, biofilm formation, and efflux pump activity are resistance mechanisms that lower the effectiveness of antibiotics. These modifications raise the possibility of treatment failure and infection recurrence in addition to limiting therapy alternatives [38].

8.3. Combination Therapy and Novel Antibiotics

Combination antibiotic therapy is being investigated more and more to combat resistance. Antibacterial activity can be droped and resistance development can be dropped by using synergistic medication combinations. Furthermore, more recent antibiotics like ceftaroline and delafloxacin have demonstrated efficacy against resistant germs, furnishing clinical settings with additional therapeutic options [39].

8.4. Role of Anti-Biofilm Strategies

Biofilm formation is one of the primary causes of chronic and persistent *S. aureus* infections. Because biofilms protect bacteria from drugs and human immune responses, infections are difficult to treat. Current treatment options include the use of biofilm-disrupting agents, enzymatic treatments, and surface-modifying approaches to prevent bacterial adherence and colonization [40].

8.5. Plant-Based and Nature Therapeutics

Chemicals originating from plants have gained attention as potential alternative therapeutic agents due to their antibacterial and anti-inflammatory properties. *S. aureus*, including MRSA strains, has been demonstrated to be inhibited by essential oils, phytochemicals such as terpenoids and flavonoids, and extracts from medicinal plants. These natural substances may work by interfering with bacterial virulence mechanisms, blocking enzyme function, or rupturing cell membranes [41].

8.6. Nanotechnology-Based Therapeutics

Nanotechnology offers novel ways to treat *S. aureus* infections. Examples of nanoparticles that can enhance antibacterial activity, reduce toxicity, and increase drug transport are silver, gold, and polymer-based nanocarriers. These technologies can more effectively target bacterial cells and penetrate biofilms, making them appealing alternatives for combating resistant illnesses [42].

8.7. Vaccine Development and Immunotherapy

Despite extensive research, there is presently no vaccine that is 100% effective against *Staphylococcus aureus*. However, research is being done on multicomponent vaccines that target surface proteins and toxins. Immunotherapeutic strategies such immunological modulation techniques and monoclonal antibodies are also being investigated to enhance host defense systems [43].

8.8. Future Perspectives

Future treatment strategies focus on bacterial virulence rather than viability to reduce the selective pressure for resistance. Quorum sensing inhibitors, CRISPR-based antimicrobial systems, and bacteriophage therapy are examples of next-generation treatments that are gaining traction. These innovative strategies could improve therapeutic outcomes and address the growing problem of antibiotic resistance [44].

9. CONCLUSION

However, due to its remarkable adaptability, diverse range of virulence factors, and increasing medication resistance, *Staphylococcus aureus* remains one of the principal pathogens of enormous medical and veterinary concern. The management and control of these germs have become particularly difficult due to the rapid emergence of multi-drug-resistant strains, such as methicillin-resistant *Staphylococcus aureus* (MRSA). Better treatment and prevention have been made possible by advances in molecular diagnostics techniques, which have made it possible to identify these germs quickly and accurately. Although there is some success with the conventional usage of antibiotics, their efficacy has been declining over time. As a result, new therapeutic approaches are being explored, some of which show great promise. Combination therapy, anti-biofilm agents, plant antimicrobials, nanotherapeutics, and immunotherapy are the most well-known. However, before these strategies can be successfully applied, much more research will be required.

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Staphylococcus aureus

PATHOGENESIS, MOLECULAR IDENTIFICATION, AND EMERGING ANTIBIOTIC RESISTANCE

PATHOGENESIS

Virulence factors, colonization, immune evasion, and disease mechanisms

MOLECULAR IDENTIFICATION

Genotypic methods for accurate and rapid detection

EMERGING ANTIBIOTIC RESISTANCE

Mechanisms, global trends, and new challenges