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Molecular and Physicochemical Studies of MRSA Resistant to Antibiotics: A Known beyond

Himanshu M. Bhogekar[1], *Ritesh P. Bhole*[2,3,*], *Pramod B. Khedekar*[1], & *Rupesh V. Chikhale*[4]

[1]Department of Pharmaceutical Sciences, Rashtrasant Tukadoji Maharaj Nagpur University, Nagpur 440033, Maharashtra, India. [2]Dr. D. Y. Patil Institute of Pharmaceutical Sciences and Research, Pimpri, Pune, Maharashtra 411018, India. [3]Dr. D. Y. Patil Dental College and Hospital, Dr. D. Y. Patil Vidyapeeth, Pimpri, Pune-411018. [4]UCL School of Pharmacy, London, United Kingdom.

*Corresponding author: ritesh.bhole@dypvp.edu.in

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ABSTRACT

As we see in the community, environment, and daily life, bacterial, microbial, and viral infection creates the severe problem. The medical field is continuously worried about the treatment of infections caused by the microorganism. Day by day, the microorganism in nature becomes stronger and gains more susceptibility to major infections. The researcher continuously works on the development of new antibiotic to break infectivity of the microorganism. But bacteria have the characteristic to adapt in a new environment by generating resistance. Many antibiotics since the discovery of penicillin work on the effects of bacteria for a short duration of time, and after that the bacteria start mutating themselves to overcome the effect of antibiotic. That stage is called antibiotic resistance. At this stage, antibiotic lose their ability to show the effect. The bacteria that show a positive response to gram stain and a negative response to gram stain both seem to be infectious. A resistant bacteria like MRSA becomes more resistant due to the constant mutation of the gene and is susceptible to causing various life-threatening infections. The antibiotics used to treat infection show a less effect at the time of treatment. The review focuses on the problems related to antibiotic resistance and its probable solution by using the derivatives of standard drugs to Methicillin resisted *Staphylococcus aureus* (MRSA) bacteria, based on MIC study reports. The information collected by referring various open-source databases such as PubMed, Chem Spider, ZINC, Google Scholar, ScienceDirect etc. from year 2005-2022.

Keywords: Antibiotic resistance, PBP2a, antibiotics, bacterial infections, MIC

INTRODUCTION

The word Bacteria has a meaningful evidential report in the Greek language. The Bacteria means “little canes or little sticks.” The “little canes or little sticks can cause disease” in plants and humans. Bacteria are ubiquitous species that adapt themselves everywhere in every natural condition due to their ability to select spontaneous mutants. It is a single-celled microorganism that lacks a nuclear membrane, metabolically active and it is divided by binary fission. *Enterococci* is a coherent illustration from a reputable member of our gut microbiome. It can turn ugly at certain fortunes[1]. The bacteria, when it becomes dangerous to the body, starts to cause clinical complications. For that purpose, the plasmids and phages (Bacterial mobilome) play an important part in circulating antibiotic resistance. Bacteria are more dangerous than the beneficent to the mortal [2]. The bacteria help to prepare the foodstuff and are susceptible to cause infection in the human habitat. The expansion of bacterial infection depends on the power of infectivity of bacteria, which is determined by comparing how many individuals are infected among the exposed ones. Secondly, the pathogenicity is counted by the capability of the organism to cause a clinical complication. The bacteria are categorized into the classes of gram-positive and gram-negative by observing the basics of their cell wall structure [3]. And by another way, one can categorize using the basics of their colony formation in availability or non-availability of oxygen, i.e., aerobic or anaerobic. Some organisms cannot be categorized by

using the basics of their cell wall structure and expansion response to the oxygen, that organism named Mycobacterium ex. *Mycobacterium tuberculosis*. Some infective organisms are categorized as the infection causing efficiency to the certain organ, like *Neisseria meningitidis* [4]. There is a variegated reservoir where the bacteria survive till it takes the entry into the host and starts the colony formation. The reservoirs are human reservoirs, animal reservoirs, arthropod reservoirs, nonliving reservoirs, etc. [5]. The transmittance of Bacteria is done by contact, airborne, droplets, vectors, and vehicular transmittance by food, water, and formite transmission [6]. To find out the transmittance frequency of methicillin permitting MecA-Positive *Staphylococcus aureus* a (Dormant MRSA), the survey was performed among health maintenance workers. 447 patient caretakers and Doctors from more than 10 common wards and ICUs were exploiters for sinusitis or throat infection that occurs due to *S. aureus* between one year when the patient was treated. Antibiotic resistance opposes the advantages, that are getting from an antibiotic. The real cause of antibiotic resistance is the overuse of stronger antibiotics to common bacterial diseases like Legionnaire's disease, meningococcal disease, fever, and strep throat infection. The treatment of general fevers and throat infections should start with first-line antibiotics like penicillin and amoxicillin, and then move on to stronger antibiotics like azithromycin and clarithromycin whenever needed. But nowadays physicians start abusing of antibiotics and making the bacteria progress towards development of antibiotic resistance. It results in bacteria start to develop resistance to the stronger and higher-class antibiotics. The major problem faced by the pharma industry is the need to develop new antibiotic for the fulfillment of requirements. At the stage of antibiotic resistance, the bacteria stay intact at the Minimum Inhibitory Concentration (MIC)of the drug. The anthropogenic antibiotic becomes the most susceptible cause of antibiotic resistance in the environment. Because, the foodstuff containing the antibiotic like garlic, honey, ginger, clove, etc. is thrown out of the antibiotic production industry. The bacteria surrounding to it makes that thrown foodstuffs feed them and develop resistance to the antibiotic present in that [7]. The factors that are responsible for the development of antibiotic resistance are categorized into behavioral and environmental/policy. The behavioral factors for the development of antibiotic resistance include the practice of prescription. The medicinal practitioners prescribe antibiotics for nonbacterial infections like common colds and flu. Sometimes senior community members self-provide the antibiotics for the normal infection without taking any consult from the physician. The second behavioral factor responsible for antibiotic resistance is hygiene and infection control options. The higher close contact with the animals, dwelling in crowded reasons, major use of contaminated items, avoidance of the cleanliness in the environment and personal life can create susceptible conditions for antibiotic resistance. Due to this practice, bacteria get the proper environment to grow, and condition to mutate themselves in the new environment. The environmental factors include the use of antibiotics in animals and plants. The higher loads of antibiotics used in agriculture for the promotion of plant growth and avoidance of diseases in agriculture. Because of higher exposure to fertilizers, the bacteria mutate themselves for living, and develop resistance. The drug development process always lies in the pipeline. Major disincentive has to be faced for the development of new antimicrobial agents. Due to the development of resistance in bacteria, epidemiologically in the year, there are 10 million persons die because of tuberculosis, malaria, cholera, diarrhea, and pneumonia. Currently, because of resistance developed to Amoxicillin, Azithromycin, and Doxycycline in *Streptococcus pneumoniae*, *Influenza A, Mycoplasma pneumoniae,* and *Chlamydophila pneumoniae* Community-acquired pneumonia become the sixth major cause of death in the USA. The European Union (EU), Iceland, and Norway published one report which includes data that shows infection caused due to resistant microorganism's records of 25000 deaths in hospital and societal costs. Again, one report published by the USA suggests that 23000 people die every year in their hospital with associated healthcare costs>$20 billion [8]. Another reason for antibiotic resistance is the prescription of higher antibiotics to children for acute otitis, which caused due to *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and non-typable *Haemophilus influenzae.* Most of the children suffered from ear infections only at the age of below 7 years. It is increasing rapidly due to resistance developed by the causative bacteria. A most famous example of antibiotic resistance is the MDR TB. Nowadays most people face the problem of respiratory tract infection, conjunctivitis, otitis, strep throat, impetigo, etc. that are caused by *Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhal,*

Streptococcus pyogenes. It happens due to the resistance developed by bacteria to the β-lactam antibiotics. Currently, people facing the issue related to suffering from enteric fever caused by *Salmonella typhi* because of 25 to 40% resistance developed to the Fluoroquinolones as well as third-generation cephalosporins [9]. The process for the development of newer antibiotics is too slow. As per the report, only two classes of antibiotics developed and marketed in the past 25 years. Novel antibiotic resistance can be developed at any time and any place. There are about 1030 thousand billion cells available on Earth that help with the mutation process in bacteria. And it helps for the horizontal gene transfer process. The event of resistance in antibiotics we can't detect at the required majority [10]. The mechanism for the transfer of resistance genes includes conjugation (the process of transfer carried out by mobile genetic element), transformation (transfer of the necked DNA), and transduction (Transfer of almost identical DNA by bacteriophage) [8].

Table (1): Duration wise development of bacterial resistance to its primary drugs [11].

Sr. no.	Name of Bacteria	Duration of Resistance developed
1	Sulfonamide and Penicillin-resistant to *Staphylococcus aureus*	In the 1930s and 1940s
2	Penicillin Resistant to *Neisseria gonorrhoeae* (PPNG) and B-lactamase-producing *Haemophilus influenzae*	In the 1970s
3	Methicillin resistant to *Staphylococcus aureus* (MRSA) and resurgence of Multi Drug Resistant *Mycobacterium Tuberculosis* (MDR-TB)	In the late 1970s and 1980s
4	*Shigella* species, *Salmonella* species, *Vibrio cholerae, E. coli, Klebsiella pneumoniae, Acinetobacter baumanii, Pseudomonas aeruginosa*	In the 1980sand 1990s

We can avoid antibiotic resistance in small amount by taking antibiotic whenever it is prescribed by a well-qualified medicinal practitioner. When he has confirmation that feedback of lower-class antibiotics is not satisfactory to the disease. Some doctors do the multifaceted interventions of antibiotics for the treatment of non-bacterial infections. If this practice is avoided, one can avoid antibiotic resistance on a major scale. The wide ecological interventions for bacteria should be avoided. If the environment arranges proper survival of the bacteria and disruption, the man should not use antibiotics to kill them. Otherwise, they may undergo mutation and develop antibiotic resistance. During daily practice, the hygienic environment concept should be adopted. Proper vaccination should be given for vaccine-preventable diseases. The government also has to make strict use of federal enactment and enforcement of regulations for the use of antimicrobial agents in agriculture. The new amendment of routine incentives and regulations should be provided [9]. The present review focuses on clinical complications caused by MRSA due to the development of resistance to various antibiotics, and to find a solution for overcoming the problems that occur due to MRSA. The concept used for finding the solution to antibiotic resistance is the repurposing of drugs by synthesizing new derivatives of Marketed drugs. The concept was elaborated by using the example of various drug derivatives and their MIC required to MRSA.

Methicillin Resistant *Staphylococcus aureus* (MRSA)

Staphylococcus aureus is an enormous bacterial human infectious agent that causes severe infections. *S. aureus* is found in surrounding and human habitats. It can cause community-acquired and hospital-acquired infections. *S. aureus* lies on the healthy human skin and mucous membranes of healthy individuals. *S. aureus* generally does not cause any harm to the skin till it enters into the bloodstream or an internal tissue. Epidemiologically, half of all adults are occupied by the *S. aureus* bacteria and near about more than 10% of people bear *S. aureus* in their anterior nares. The problems caused by *S. aureus* in humans are like as bacteremia, skin and soft tissue infections, impetigo, infective endocarditis, carbuncles, folliculitis, osteomyelitis, furuncles, scalded skin syndrome, cellulitis, septic arthritis, prosthetic device infection, pulmonary infection, gastroenteric, meningitis, toxic shock syndrome and urinary tract infection [12]. The special antibiotic used to treat; the infections

caused by *S. aureus* is β-Lactam antibiotics. It is principally targeting the Penicillin Binding Protein (PBP2a) to show its bactericidal action. Due to higher exposure to the antibiotic, it shows resistance toward drugs and keeps infection-causing ability intact [13]. Methicillin is a key antibiotic that inhibits the PBP2a. The PBP2a is a protein that takes part in the process of cell wall development [14]. Methicillin resistance was observed because of over action of methicillin hydrolyzing β-lactamase enzyme and due to over-rated action of PBP and PBP2a proteins [15]. Methicillin keeps the development of PBP and PBP2a protein below level, but the mutation that is observed in the genome of proteins becomes the enhancer to the development of resistance. The MSSA isolates itself from MRSA only by gene coding. The MecA gene codes 76 KDa Penicillin Binding Protein (PBP2a) [16][17]. The MecA gene is obtained through *Staphylococcus sciuri7*. ccrA and ccrB were found at the Mec gene. Other than MecA on the staphylococcal chromosome, there are other two different genes i.e. MecR1 and MecI that are co-transcribed disparately to MecA. MecR1 helps for signal transduction and MecI works for the transcription process [18]. Homogeneous resistance is because of an alteration in gene sequence at a particular location. Other than these factor that lie internally and externally show effects on methicillin resistance. The internal factors that interrupt the effect of the MecA or over-expression of PBP2a help in the development of methicillin resistance. Fosfomycin, β-Chloro, D-alanine, and D-cycloserine help in the reduction of methicillin resistance. The External agents that show involvement in the development of methicillin resistance are swab attention, pH, medium composition, osmolarity, and temperature. Full growth of the external agents utilized in a medical laboratory for enhancement of new searching of strains that evident from general methicillin resistance; segregates are developed in the presence of NaCl solution at a temperature range of (30-35˚C) [19]. A resistance to methicillin was developed due to the interspecies repetition of the MecA gene in a heritable *Staphylococcus* species to *Staphylococcus* mutated species by a unique staphylococcal inheritable element. Till 1961 all the *S. aureus* strains were mthicillin susceptible but when people started to use methicillin, the situation get changed, all strains started to make themselves as MRSA [20]. Methicillin in 1950 was first incorporated into the lethal drug category whenever it was used for the treatment providence of penicillin-resistant staphylococcal complications [21]. MRSA can be categorized into HA-MRSA and CA-MRSA. In 1990 MRSA seemed to be the main cause of nosocomial infection. Resistance power develops to the antibiotics and helps bacteria to survive in exposure to antibiotics too [12]. The HA-MRSA is the lowest surviving strain. It is survived when the antibiotic exposure is too much lower. The CA-MRSA strain counts in the category of higher infection causal strain. Particularly in skin and soft tissue infections and dangerous infections having similarities like necrotizing pneumonia, necrotizing fasciitis, and myositis. The enhanced CA-MRSA clinical complications commonness could be ascribed to the development of natural surveillance, enhanced transmission, higher colony formation, reduced bacterial entrance to flare acridity genes, and enhanced disease causal capability at the time of infection. CA-MRSA dominates itself to cause skin infections [22].

PBP2a: Drug target for the antibiotics

The Penicillin Binding Protein 2a (PBP2a) consists of two chains, namely chains A and B. The resolution and R-value of the protein molecule were 1.60 Å and 0.202 Å. A total 359 of amino acid residues were found to be in the most favorable region. 6 unique ligands were present in chains namely chloride ion on 404 B and 406 A, glycerol on 407 B, sulfate ion 402 A and 402 B, sodium ion 405 and 406 B, zinc ion 403, 404, and 405 A and 403 B, ceftobiprole on 401 of both [23]. A recent study has confirmed that following all residues Ser 75, Ala 182, Phe 241, Ser 262, and Arg 300 are crucial for binding with minocycline HCl [24]. The cell wall-producing enzymes with penicillin sensitivity are focused on the β-lactam antibiotics. Their propensity to bind radio-labeled penicillin makes them easily detectable [25].The Penicillin-Binding Proteins (PBPs) are historically divided into a molecular mass or molecular weight, Penicillin-Binding Proteins (PBPs). High molecular weight Penicillin-Binding Proteins (HMW-PBPs) are divided into two categories. One is class A, and the other one is class B. Low-molecular-weight PBPs (LMW-PBPs) are also divided into four subclasses, and they have a tertiary structure. Penicillin-Binding Proteins with high molecular weight are required for mobile survival and are vital to mobile survival, which is the actual target of β-lactam

antibiotics. When the Class A Penicillin-Binding Proteins (PBPs) catalyze the biosynthesis of a specific linkage of monosaccharides called the O-glycosidic linkage of monosaccharides, the reaction we also called trans glycosylation. Each category of Penicillin-Binding Proteins, namely category A and category B causes cross-coupling reaction to catalyze during peptidoglycan biosynthesis [26]. PBPs have transpeptidase or carboxypeptidases in their Penicillin-Binding domains, which are involved in peptidoglycan metabolism. Those Penicillin-Binding Proteins, which have a low molecular weight, are not necessary for laboratory stipulations, so it signifies very few antibiotic goals that consist of β-lactam antibiotics [27]. The Penicillin-Binding Proteins contains a donor strand. The D-Ala-D-Ala residues of the 'Donor' peptidoglycan strand are hydrolyzed at the ends of amino acid chains as an acyl intermediate which is generated between the carbonyl of the penultimate D-Ala and the active site serine of the Penicillin-Binding Proteins. The 'Donor' peptidoglycan binds to PBP so that the D-AlaD-Ala moiety is vulnerable to assault by the PBP active site's nucleophilic serine hydroxyl group. All bacteria contain PBPs. However, size, number, quantity, and affinity of β-lactam antibiotics differ from one species to the next. When we are talking about *Staphylococcus aureus*, we are talking about gram-positive bacteria. Scientists differentiate between gram-positive and gram-negative cells based on a cell's core component. Peptidoglycan is a significant factor in determining whether bacteria are gram-positive or gram-negative. When we talk about core components, we know that peptidoglycan is the core and central part of the bacterial cell wall. When we think about the mechanochemical properties of the bacterial cells and the pressure potentials, the highly complex multicomponent structure present in the cell wall is known as peptidoglycan. And it is required for movement (mechanical) strength, which counteracts the intracellular pressure of bacterial cells. As the peptidoglycan is a core component of the cell wall, it is responsible for forming a continuous, mesh-like structure around the bacterial cell membrane, which protects cells from destruction. Thus, peptidoglycan plays a vital role in the biosynthesis of the cell wall for *S. aureus* bacteria and many other gram-positive bacterial cell walls. Peptidoglycan is also called murein, glycopeptide, or mucopeptide. Peptidoglycan is a polymer made up of long glycan chains connected by a flexible peptide bridge [28]. A cell wall is present around the cytoplasmic membrane to maintain the pressure inside the bacterial cell and prevent the leakage of essential components from being leaked through a semipermeable membrane. The pressure inside the cells helps to protect the cellular contents from external environment, and thus it is helpful to balance shape of bacterial cell. The bacterial cell layer gives desired auxiliary astuteness for bacteria or microbes, which then helps to resist osmotic pressure differences between the cell divider and the exterior of the cell. We conclude that the bacterial cell wall is a crucial component for differentiating distinct strains of bacteria. It is reported in various papers that gram-positive bacteria contain folds of the cell wall; approximately 20-fold thicker cell walls are about 15-80 nm. The cell wall is responsible for maintaining bacterial strength by simply managing microbes' shape, size, and integrity. The core component of the bacterium is peptidoglycan, a macromolecule composed of O-glycosidic linkages of main monosaccharides (glycan strands). This is then cross-linked through movable and species-specific peptide bridges required to produce a mesh-like structure surrounding the bacterial cell. Glycan strands are repeating units of N-acetylglucosamine (GlcNAc) and N-acetylmuramic acid (MurNAc) amino sugars that are then attached with β-(1,4) glycosidic bonds in an alternating manner. Each N-acetylmuramic acid (MurNAc) residue is connected to short amino acid chain; L-alanine, D-glutamine, L-lysine, and D-alanine, which are in contact with pentaglycine bridges, and these cause crossbridge formation. MurNAc and GlcNAc pentapeptides are used for peptidoglycan biosynthesis. To give better mechanical strength and flexibility throughout entire cell cycles of bacterial life cycles, bacterial growth occurs when bacteria get what they need for development. Crosslinking and glycan polymerization are two reactions. They are two enzymatic activities. Both of them are required for cell wall biosynthesis. Transpeptidase enzymes subsequently cross-link the polymerized glycans by forming amide bonds between bound peptides [29]. β-lactam antibiotics act like suicide inhibitors and they bind to PBPs. Their mechanism is explained as; the active site serine cleaves the β-lactam ring's carbonyl, causing the ring to open, which results in a covalent acyl enzyme complex forming. This product is eventually hydrolyzed, thereby inhibiting additional reactions [30]. The response in which core components are formed leads to the generation of a backbone called stem peptides. In this phase, amino acids are cross-coupled and create peptidoglycan, and this phase occurs in the outer cytoplasmic membrane; therefore, we

call it as a transpeptidation reaction. The Penicillin-Binding Protein (PBP2) of *staphylococcus aureus* are an enzyme that is involved in the final step of peptidoglycan assembly. It is a crucial factor in the pathogen's virulence factor. PBP2, a class A enzyme in *Staphylococcus aureus*, needs its ligand to localize to the septum as well as engage in the division of cells. Undecaprenyl N-acetyl muramic acid (UDP-MurNAc) is a pentapeptide, which is then shifted to Undecaprenyl phosphate (UNDP) via the Mur Y enzyme, which works as a membrane-associated carrier. Mur G is a peripherally membrane-associated protein to which GlcNAc is coupled and is responsible for producing Lipid II.

Structure of tet(R) gene

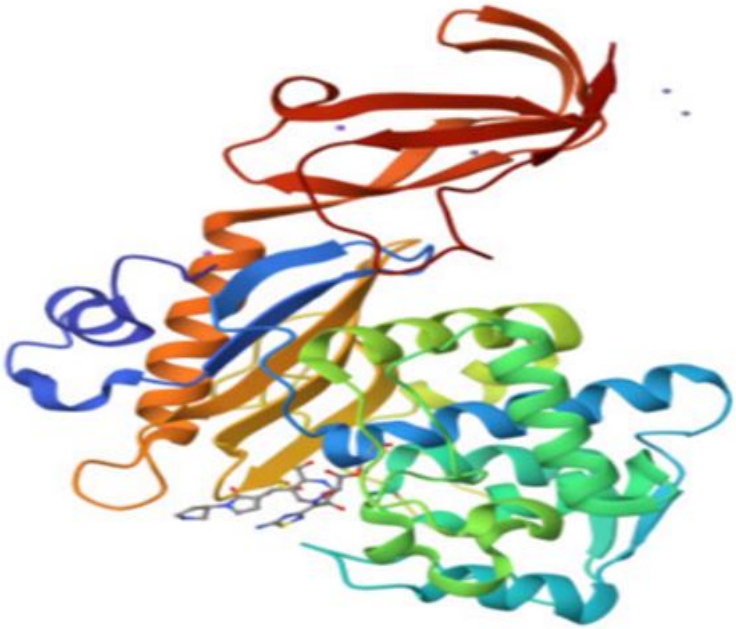


Figure (1): Crystal structure of PBP2a which having 2 chains (Chain A & B).

The target suitability can be checked by performing an in-silico study such as docking and Molecular Dynamic Simulation (MDS). From docking, the better understanding can gain related to interaction of synthesized derivatives of standard drugs with amino acids. For example, isoxazole-carboxamide derivatives use as an antimicrobial agent against gram-negative bacteria like *P. aeruginosa* (targeted protein elastase B, PDB:ID 1U4G), *K. pneumonia* KPC-2 (targeted protein carbapenemase, PDB:ID 2OV5). It conforms that synthesized isoxazole-carboxamide derivatives are suitable for antimicrobial action by calculating Root Mean Square Deviation (RMSD) of their docked score.

Table (2): RMSD values of isoxazole-carboxamide derivatives to various bacteria.

Sr. No.	Name of Bacteria	Targeted Protein/PDB:ID	RMSD
1	*P. aeruginosa*	Elastase B/1U4G	0.90
2	*K. pneumonia*	Carbapenemase/2OV5	1.40

The calculated RMSD for isoxazole-carboxamide derivatives found to be less than acceptable limit 2.0. that's why the isoxazole-carboxamide derivatives shows accurate bonding with target and shows the susceptible antimicrobial effect [31].

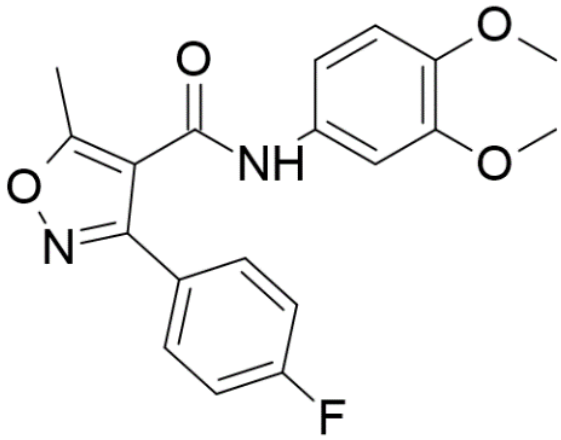
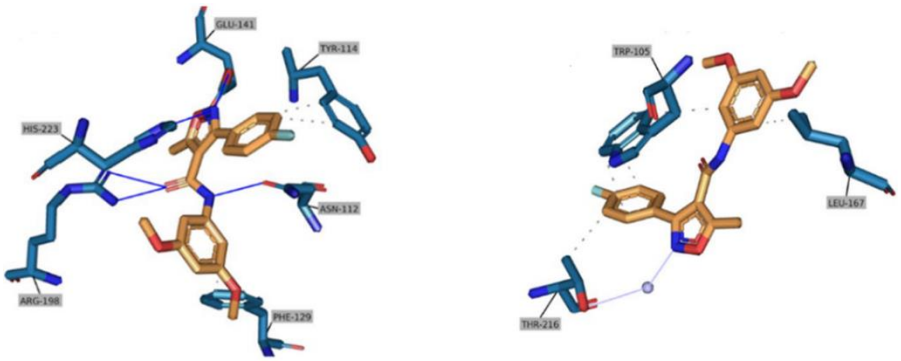


Figure (2): Isoxazole-carboxamide derivative used for docking to targeted of protein of bacteria.



A B

Figure (3): Interactions of amino acids with Isoxazole-carboxamide derivative.

A: Interaction with Elastase B/1U4G of *P. aeruginosa* interactive residues are GLU-141, TYR-114, HIS-223, ARG-198, PHE-129, ASN-112.

B: Interaction with Carbapenemase /2OV5 of *K. pneumonia* interactive residues are TRP-105, LEU-167, THR-216.

Mannich bases of 7-piperazinylquinolones and kojic acid derivatives used as an antibiotic. Molecular docking of Mannich bases of 7-piperazinylquinolones and kojic acid derivatives to the *S. aureus* bacteria having nucleic acid Topoisomerase II (PDB:ID, 2XCT) shows the promising result. RMSD for the compound used for docking was found to be less than 2[32].

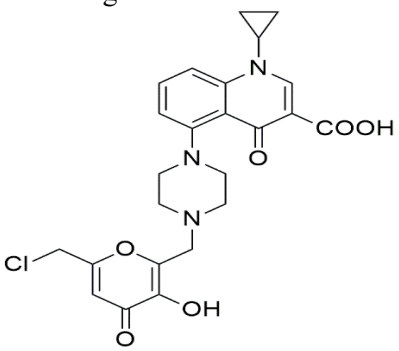


Figure (4): Mannich base of 7-piperazinylquinolones and kojic acid derivative used for docking to 2XCT

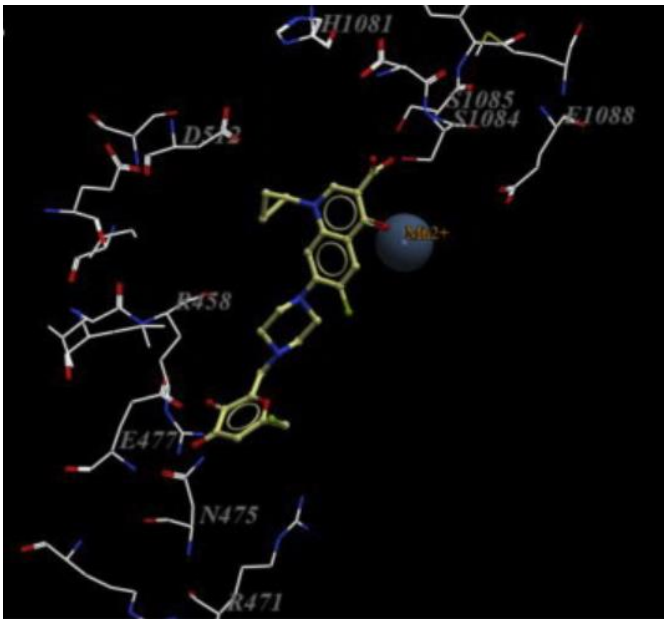


Figure (5): Docked conformation of Mannich base of 7-piperazinylquinolones and kojic acid derivative in the binding site of topoisomerase II DNA–gyrase.

Staphylococcus chromosome Cassette

The MecA gene which involves the PBP2a formation founds in all MRSA-strain. The blaZ gene decodes the Penicillinase enzyme while the MecA gene decodes PBP2a located in the SCCMec gene. Recent research elevates that granting of MecA gene alteration has a dominating effect on the condition of MecA and PBP2a, which have very low results on the location of β-lactam resistance. The MecA gene amongst 17 clinical MRSA clones was set up to have the heterogeneousness in gene sequence and/or relinquish in the sequences, but the gene sequence was exclusively heterogenic to every SCCMec gene, and had the exception for SCCMec III. It can be described using a genetic arrangement that isolates itself because of one or two extraordinary base negotiations. The MecA gene in the one SCCMec II clone has a G to A negotiation located at 25 bp upstream position of the MecA. Three out of six SCCMec IV clones (C103, M153, and V043) have a G to T negotiation in the ribosomal gene sequence. Hence there is difference in two classes of genetic arrangement in this SCCMec type. The MecA gen of the 7thSCCMec, 5 clones are able to separate into two different classes of whole 7 clones which have a C to T negotiation at 33rdpositions, while three of the clones possess new A-G negotiation at location 38th[33][34]. The complex gene for PBP2 and MecA, was currently developed through a MRSA medical separation. The effort of these genes was boasted to changing a methicillin-susceptible host *Staphylococcus aureus* clone to a methicillin-resistant strain. It has long been identified that methicillin resistance is starts to be unstable at the time of more exposure to culture in a drug-less medium. The whole methicillin-resistant *Staphylococcus aureus* (MRSA) clones are examined. They possess the MecA gene, a 2130bp stretch of DNA for non-staphylococcal inception which has the affiliation along with greater block ranges to 40-60 kb of outer DNA, which is clinched into the Staphylococcal chromosome. MecA codes to 78 Kb Penicillin Binding Protein (PBP2a) which possesses distinctly less relation for lactam antibiotics. The sequence of the MecA gene clone has a structural pattern and attribute of cell wall generation transpeptidase. In case of identification of the relevant contributing factors involved in the methicillin resistance, one can find phenotype jumping genes sequence alteration i.e. (Tn557) which is formed in the isogenic origin of a highly resisted MRSA strain. The transposon unwinding trials show that activity of MecA gene and subsidiary genes are both necessary for activation of high-located methicillin resistance. The MecA gene is a segment of 21-60 kb Staphylococcal chromosomes. A little changeable thing is that it also possesses an inheritable complex like Tn554, pUB110, and pT181, which provide resistance to non-β-lactam antibiotics. The current consent model of MecA ordinance contains two principal route (i) Gene list of the β-Lactam antibiotics to outer cellular detector sphere of MecR1 of

the sensor inducer and activation of the cytoplasmic debase sphere, which materialize to be a PR metalloprotease; (ii) the accelerometers debased sphere of MecR1 either straight cuts the promotor compelled MecI dimer or initiates the repressor fractionalization. It paralyzes the power of repressor protein to dimerize and stick to MecA gene, which enables the activation of the resistant gene. The MecA origination perpetuates along with availability of the drug. The initiation of MecA is due to MecR1 which has been characterized as very-very moderate so that the cells accomplishing with whole MecR1 and MecI shows malignancy of MecA gene which is called pre-MRSA phenotype. It has been presumed that more resistance towards β-lactams, which is a feature of various current MRSA medical clones implies a non-functional MecR1 and MecI executive system. MecA executive location is nothing but the 3-component system which has MecR1 and MecI genes, the MecR2 gene is co-translated along with MecR1 and MecI. The In-vitro and In-Vivo purification checking displayed that MecR2 functions as an anti-repressor by dealing directly with the MecI repressor. Disturbance to the MecA gene affects its non-functionalization mode by proteolytic fractionalization. In the MRSA clone along with activated MecR1-MecI genes, the MecR2 is necessary to complete the activation of MecA recap. A reimbursement to the hamstrung initiation of MecA by MecR1 permitting the normal exploration of β-lactam resistance.

The MecR2 Interaction:

The MecR2 correspondent to the translating repressor of the xylose operon that has an N-terminal of DNA binding sphere and a C-terminal dimerization sphere. The mode of action for MecR2 possesses the straight contact with the MecI dimer. Ultimately interpose along with its gene list to the MecA promoter [35].

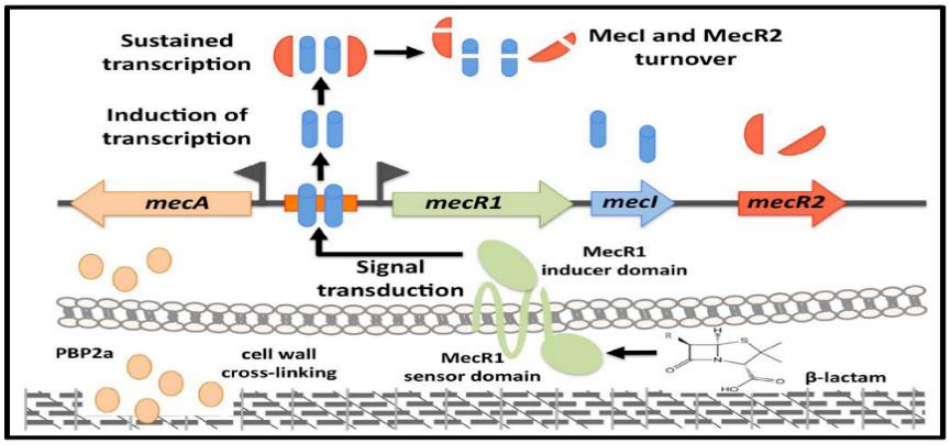


Figure (6): Genetic Activation of MRSA

The MecR2 obstructs along with the gene list of MecI and MecA in an imperative way. The MecR2 can be oligomerized in an imperative type and restrict the interference with MecI. The MecI and MecR2 are translated through the MecR1gene as like to the cellular counts of MecrR1 and MecI proteins. MecR2 functions like an anti-repressor, which disturbs the gene list of both proteins. The cutting of the MecI sequence seen at the time of MecA initiation, which alternated with the actual MecR1, degraded sphere and became a consequent task which not claimed for the initiation of MecR2. By interfering with MecI and disrupting its gene list, the MecA gene cherishes an actual disruption of MecI-MecR2 dimer by preparing the bonds highly permissible to proteolytic inactivation. The MecR2 retroactively pays to the MecR1 alternated initiation of MecA, which is essential to the normal activity of β-lactam resistance. It manages the complete initiation of the MecA gene due to harsh type MRSA clone, which is positive to the MecR1-MecI interaction. And become also positive to the MecR2 clone. These clones are susceptible to expression in normal conditions of β-lactam resistance. The MecA is effectively persuaded on exploration towards β-lactams with its 3-component system. The MecR1 no longer stays activated and forms a steady MecI dimer and remaining replica of MecR1 on the cell membrane, and free MecR2 vanishes by the protein synthesis pathway.

Clinical Complications associated with MRSA

The *S. aureus* is among the principal inception to the Community-acquired, Healthcare related and Hospital-acquired infection [36]. Hospital-acquired SAB patients along with intraventricular device-assisted complication, wound sepsis, or nosocomial pneumonia admitted due to numerous reasons and inherent situations that can be highly affected by distance of staying and existence. *Staphylococcus aureus* can be the continuous cause of Healthcare assisted fever [37]. CA-MRSA complications seem to initiate in normal individuals who do not possess the traditional risk agents for MRSA [38][39].

Endocarditis: The *S. aureus* has the ability to cause infections in the endothelium of heart. A viewpoint of infectious endocarditis should be contemplated in this type of case with furnishing the threat agent, heart murmurs, vasculitis, and embolic marvels related to the infectious endocarditis[40]. The changing lifestyle gives rise to the decadence of valvular complaints. The *S. aureus* is nothing but the continual causal agent in the infectious endocarditis. The mortality reporting in these cases is more than the HIV patient. Despite the fact, the mechanical heart faucets are probably at improved threat for complication than the bio-prosthesis in the first three months [41]. The patient suffered during the two months following surgery is known as the prosthetic-stopcock endocarditis and is normally gained in the sanitarium [42]. The general stopcock endothelium is variably resistant to the infection. The mechanical lesions of this endothelium are the results of exploration of the underpinning extracellular matrix protein. The original inflammation, depot of the fibrin and the platelets, form a nonbacterial thrombotic endocarditis (NBTE) which is vulnerable to colony formation. Infectious endocarditis can be done devoid of recognizable preceding stopcock lesions. This is exactly accurate for *Staphylococcus aureus*, which poses the surface as the principal cause of infectious endocarditis in recent times [43].

Impetigo: Impetigo is originating from β-hemolytic streptococci or *Staphylococcus aureus*. The fatal skin allows bacterial colony formation. Extra growth of the bacteria originates skin problems, i.e., bullous impetigo and simmered skin patterns, which caused due to staphylococcal toxins and toxic shock patterns, initiated by the Staphylococcal and Streptococcal toxins. It is the exemplifications of toxin intermediate of *Staphylococcus aureus*. It continuously initiates in a healthy child from inside of skin in a flashy manner. Bullous impetigo is nearly as broad, originating from one organism. *S. aureus* considerably associates with group II, having the phage type 71. The *Staphylococcus aureus* creates a depilated toxin which are protease that widely hydrolyzes intracellular adhesion nodes, Desmoglein-1, which is available in the desmosomes of the keratinocytes located above the upper skin grainy subcase. There is a minimum of 2 distinguishable types of depleted toxin, toxin A related to bullous impetigo, and toxin B, which stewing the skin pattern. The clone of *Staphylococcus aureus* spreads the depleted toxin, which is continuously protected to the patient suffering from impetigo. Bullous impetigo arises more normally in an internal region which is similar to the dipper area, axillae, and neck although the cutaneous region may be damaged, again it may include the triumphs and soles, etc. [44]. Impetigo is a major contagious complication, along with straight proximity between the main way of spreading. The beginning of the skin complications is initiated through the ETA and ETB, which are functionalized serine proteases generated from some of the clones of *S. aureus*. The ETA is decoded on the stage of prophage while ETB is decoded on a major penicillinase type plasmid. The ETA and ETB lead to upper skin fractionalization, from which the results on desmoglein-1 are known as the desmosome adherent. This type of fractionalization is directly related to the medical personification of the blistering skin complaint found in *Pemphigus neonatorum* and/or nonspecific Staphylococcal stewing skin patterns [45].

Folliculitis: The Folliculitis decalvans is an infrequent inflammation. *Staphylococcus aureus* and an inadequate entertainer of unprotected reply sense play the most important role in the building of this inflammation. The lesions occur principally in the vertex region and the ocipitalaria. *S. aureus* appears to play a key role in the pathogenesis of folliculitis declavans. It may be found majorly in each case that suffered from undressed folliculitis declavans. It has been predicted that "Superantigens" or cytotoxins can attached to the high histocompatibility complex of class II molecules. It can trigger the T-cells, although can escape the investigation from the host's inadequate system. It depicts

the key role in the pathogenesis. The patients periodically describe mechanical bleeding as well as rigid complications like Pain, Itching, as well as burning sensation[46]. Rarely this prognosticate susceptibility has been changed, due to the Methicillin-Resistant *Staphylococcus pseudintermedius* (MRSP) as well as Methicillin-Resistant *Staphylococcus aureus* (MRSA) which gets the other current in canine SBF patients [47].

Toxic shock Syndrome: The multiple health complications of Staphylococcal complaints and the hike in the number of gram-positive infections, which involves the sanitarium as well as community-acquired Methicillin Resistant *S. aureus* (MRSA) complication. The *S. aureus* develops a variability index for the protein exotoxins, which are significant for grasping pathogenesis of TSS. This type of bacterial toxin involves Staphylococcal endotoxins, as well as the Staphylococcal enterotoxin-like toxin. Toxic Shock syndrome is nothing but the monogenic complications that are normally available along with inception of fever, hypotension, and continual multiorgan complication to the event of several minutes. In spite of the fact that, highest parts of toxic shock syndrome are menstrual assisted. Another accepted root of the toxic shock syndrome is, *S. aureus* involves in a surgical injury. Soft tissue infections involve infected becks, postpartum complications, intrauterine complaints, nasal packs, and pneumonia. The autopsy of toxic shock syndrome is the major normal cause of alternate autopsy of day as well as can be related to a benign crack[48].

Urinary Tract Infection (UTI): Urinary Tract Infection (UTIs) is one of the major frequent infections of the urinary tract. It is greeted in the medical health practice. It is the major frequent type of Nosocomial infection in the US. The *S. aureus* has been known for its period of infrequent urinary insulation. Classically, the *S. aureus* has been contemplated by foreplay, in order through blood route by practicing internal and external ulcers. In vitro, the *S. aureus* is susceptible to binding with the complete uroepithelial tissues from the glycoproteins set up in the urinary bladder as analogous to GP51, which is notably growing in the availability of urinary tract infection [49]. Previously in the bladder urine, the bacteria can be rejected through the bladder protection mechanism and it can segregate to foreplay the bladder wall and evolve in infection. The power of bacteria to evolve, multiply and cause complications is not entirely found in distinct characteristics of the bacteria. Enterococci establish a bunch of gram-positive Streptococcus species.

Necrotizing fasciitis: The life-converting complication that needs a complex surgical or clinical-related situation and the pressured agent involves in previous MRSA complication. As like hepatitis C, diabetes mellitus, cancer, and HIV infection [50].

Pyomyositis: Pyomyositis was originally accepted as an equatorial disease it is now perceived in the region of high-temperature weather and mainly in the person who is an HIV intravenous drug user [51].

Necrotizing community-acquired pneumonia (CAP): It is related to influenza and it is normally reported in the primary fit new children. At the time of 2003-2004, 15 patients of MTSACAP along with 4 expiries of the patient, with a casualty rate of 26.7 noted throughout the 9 countries. Necrotizing pneumonia is descripted by pulmonary inflammation along with supplemental necrosis as well as multiple small depressions. The unavailability of the blood flow towards the blood-perfused area obstructs the dose of antibiotics and causes unrestrained complication or other damage to the lung tissue. Pulmonary gangrene is nothing but the last phase in sequence of improving enfeeblement of pulmonary parenchyma which is judged through the “chucking of the pulmonary lobe” [52].

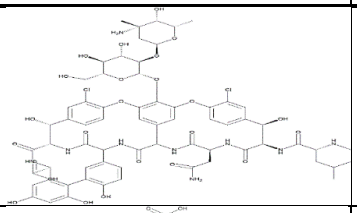
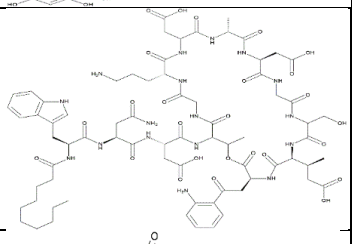
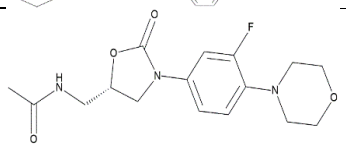
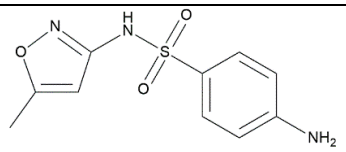
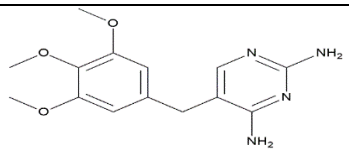
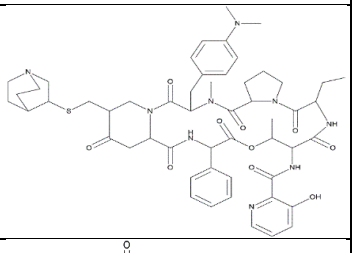
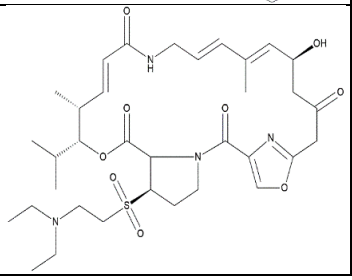
Septic arthritis and osteomyelitis: It may occur due to the direct abrasion and a complication occurs due to the *S. aureus* infection. The osteomyelitis may be staying mature and asymptomatic to the multitudinous period, prior to refreshing begin of medically characterized osteomyelitis. Habitual osteomyelitis creates intermediate bone analgesia, humanness and disgusting effluent accompanied by a time of dormancy. Sometimes the effluent is intact. In spite, small septic arthritis is a popular problem of small osteomyelitis [53].

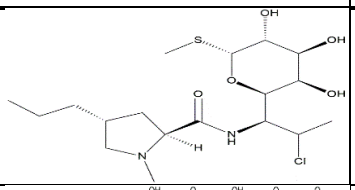
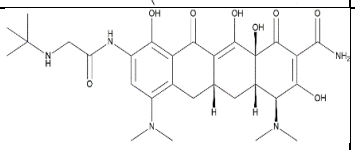
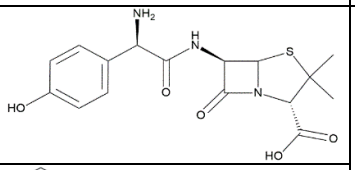
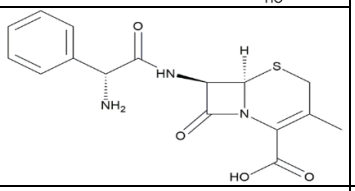
Sepsis: It is a water house of Friedrichsen manner which is indicated as petechial rash, coagulopathy, cardiovascular collapse, and bilateral adrenal hemorrhage. sepsis is nothing but the clinical exigency that explains the body's systemic immunological response towards an infectious operation. It tends to last phase of organ dysfunction and leads to death. The time of incidence is critical sepsis and septic shock in the US, which is 300 patients per 1000 people. Sepsis is the major health caretaker difficulty in the US. The computation for sepsis was 20 million in 2011 alone [54].

Antibiotics used to treat the complication caused by MRSA

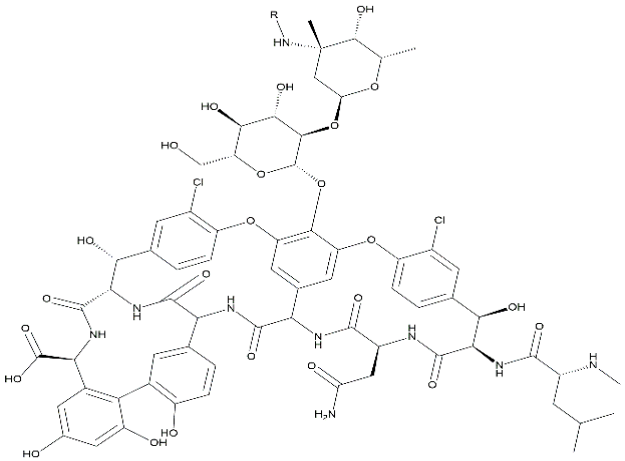
To treat the above infection some discovered drugs used, they are as follows:

Table (3): Various antibiotics to MRSA

Sr.no.	Class	Name of drug	Structure	Reference
1	Glycopeptide antibiotics	Vancomycin		[55]
2.	Cyclic lipopeptide antibiotics	Daptomycin		[56]
3.	Oxazolidinones	Linezolid		[57]
4.	Sulfonamides	Sulfamethoxazole		[58]
5.	Folic acid inhibitors	Trimethoprim		[59]
6.	Streptogram-positivein antibiotics	Quinupristin		[60][61]
		Dalfopristin		

Sr.no.	Class	Name of drug	Structure	Reference
7.	Lincomycin antibiotics	Clindamycin		[62]
8.	Glycylcycline Antibiotics	Tigecycline		[63]
9.	β-Lactum Antibiotics	Amoxicillin		[64][65]
		Keflex		
10.	Combination of Glycopeptide and β-Lactam Antibiotics	Amoxicillin + Vancomycin		[66][67]
11.	Combination of Cyclic lipopeptide and β-Lactam Antibiotics	Amoxicillin + Daptomycin		[68][69]

All the above drugs are basically used for the treatment of diseases caused by MRSA. But from the above list, many drugs suffer from resistance to MRSA. They do not show a proper effect at the time of treatment. And that's why the phenomenon of repurposing of drugs by synthesizingnew derivatives of existing drugs can be used. From the study, it is found that the derivatives of marketed drugs seem more susceptible than the standard drugs.



a. R = H

b. R = $(CH_2)_2$-NH-$(CH_2)_9$-CH_3

Figure (7): Chemical structure of vancomycin with its substituents

Table (4): Effect of Vancomycin derivativesto MRSA

Sr. no.	Derivative Code	MIC (µM)
		***S. aureus* ATCC 33591**
1	a	0.67
2	b	0.42

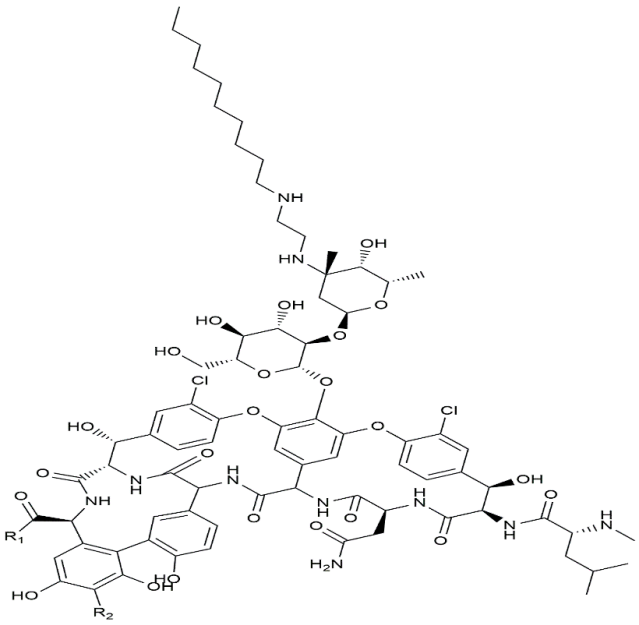
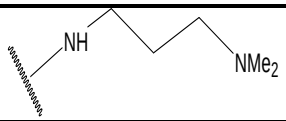
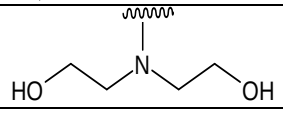
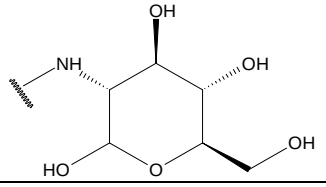
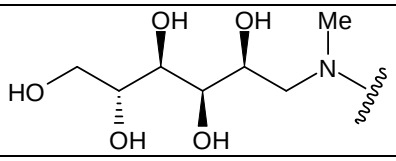
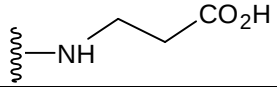
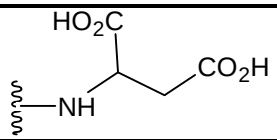
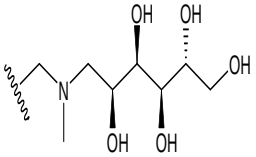
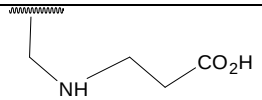
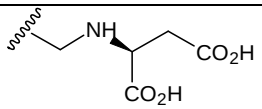


Figure (8): Chemical structure of b derivative of vancomycin.

Table (5): Effect of R_1, R_2 substituted b derivative of vancomycin to MRSA

Sr. no.	R_1	R_2	MIC (µM)
			***S. aureus* ATCC 33591**
1		H	0.87
2		H	0.69
3		H	0.44
4		H	0.11
5		H	0.11

Sr. no.	R_1	R_2	MIC (µM) *S. aureus* ATCC 33591
6		H	0.28
7	OH		0.65
8	OH		0.16
9	OH		0.28

From the Above data ofR_1, R_2 substituted b derivative of vancomycin, it is observed that, MIC required for vancomycin is 0.67 µM. However, the MIC required for derivatives of vancomycin is less than the standard drug. So, the derivatives can work effectively as compared to the standard drug. And it helps to overcome the problem of vancomycin resistance to MRSA [70].

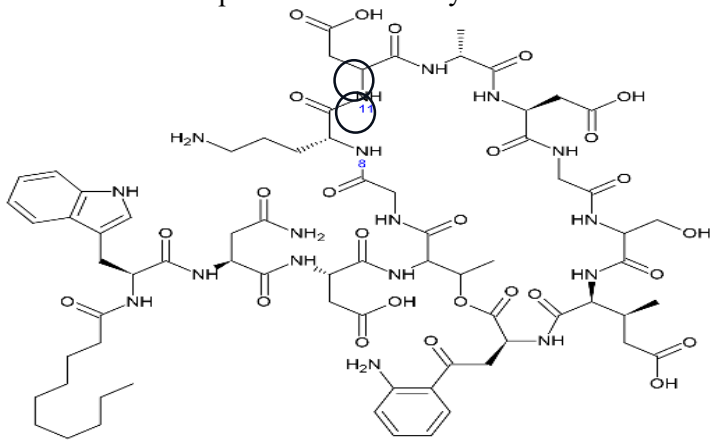
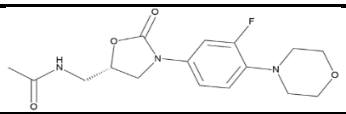
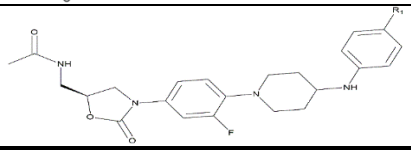


Figure (9): Structure of Daptomycin showing 8th and 11th position for the substitution.

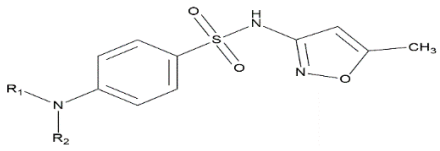
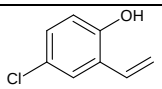
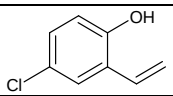
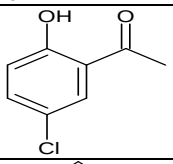
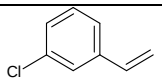
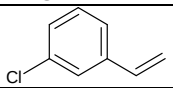
Daptomycin shows resistance to MRSA. But the cationic residues if attached on amino group present on 8th and 11th position, it is predicted that the daptomycin shows good activity to resistant bacteria [71].

Table (6): Effect of Linezolid derivatives to MRSA

Sr. no.	Parent structure with position of substitution (R)	-R Substituent	MIC (µM) *S. aureus* MRSA
1.		No substitution	2.96
2.		-F	1.16
		-Br	1.01

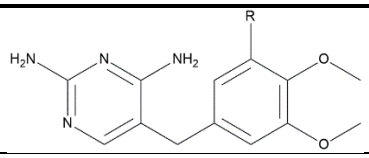
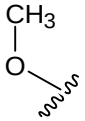
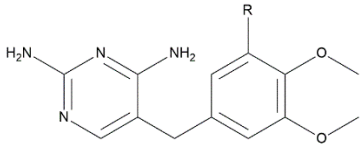
As observed in the above table, the activity of linezolid derivatives is more than the standard linezolid drug. The MIC required for linezolid to MRSA was 2.96µM, but when it was converted to its derivatives, the MIC reached down to less than 2.96µM. It means that with the proper substitution on proper position drug becomes susceptible to avoiding antibiotic resistance [72].

Table (7): Effect of Sulfamethoxazole derivatives to MRSA

Sr. no.	Parent structure with position of substitution (R)	-R Substituent		MIC (µM)
		R_1	R_2	*S. aureus* MRSA
1.		H	H	62.5
				15.62
		H		15.62
				31.25

The above data shows that sulfamethoxazole has its own MIC 62.5 µM. But nowadays it shows the resistance. So, to overcome this problem derivatives of sulfamethoxazole can be utilized. Above derivatives show more potency to MRSA. And it conforms from MIC of derivatives. All the MIC of derivatives is lesser than standard sulfamethoxazole [73].

Table (8): Effect of Trimethoprim derivatives to MRSA

Sr. no.	Parent structure with position of substitution (R)	-R Substituent	MIC (µM)
			*S. aureus*ATCC 29213
1.			17.22
2.		R =	MIC (µM)
		Cl	4.24
		Br	4.24
		I	4.24

From the above table it is seen that standard trimethoprim has a MIC17.22µMand derivatives of standard trimethoprim give an MIClesser than standard drug. It is 4.24 µM for all three derivatives. So, from this, it can be said that derivatives are helpful in avoiding resistance [74].

Minocycline susceptibility to MRSA

The MRSA shows a resistance to most of the antibiotics. The minocycline is counted under the family of tetracycline. Which has a nucleus of four cyclic rings. Whole tetracyclines are mildly bitter and possess slight solubility in water, but hydrochloride salt possesses most solubilityin the water. The minocycline in the tetracycline family works as a bacteriostatic agent. It shows susceptibility towards binding with 30sribosomal subunit and disrupts protein synthesis. The minocycline can be used in dermatitis, periodontal diseases, rheumatoid arthritis, CNS pathologies, neuropathic pain, ischemia, atherosclerosis, inflammatory bowel disease, allergic asthma, autism, osteoporosis, etc.

[75]. The minocycline considered a highly lipophilic molecule can effectively surpass Blood-Brain Barrier and blocks different gram-positive and gram-negative bacteria[76].

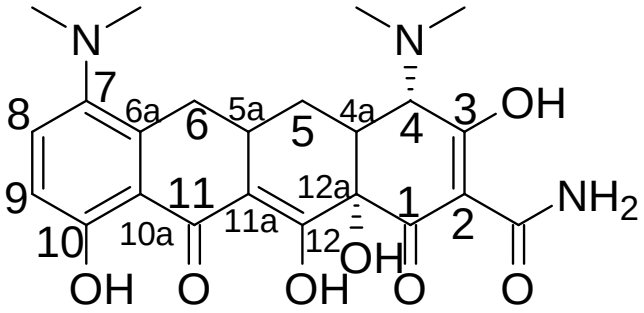


Figure (10): Chemical structure of Minocycline

In Minocycline, amide group is present at 2nd position of A ring, four Hydroxy groups are located on 3rd position of A ring, 12th position of B ring, 10th position of D ring, and last at the fused position of A and B ring i.e., on 12tha position. The two ketone groups are present on 1st position of A ring and 11th position of the C ring.Two disubstituted amino groups are located on the 4th position of A ring and 7th position of the D ring. The replacement of amide with aldehyde or nitrile abolishes the activity. Slight modifications in A ring can be possible at the 3rd position. The presence of Dimethylamine group at 4th position is necessary for an antibacterial activity. The ring structure possesses upper and lower periphery region. With the modifications done at upper periphery, the lipophilicity of drug can be enhanced particularly at 7th and 9th position which helps to detect target quickly [77].

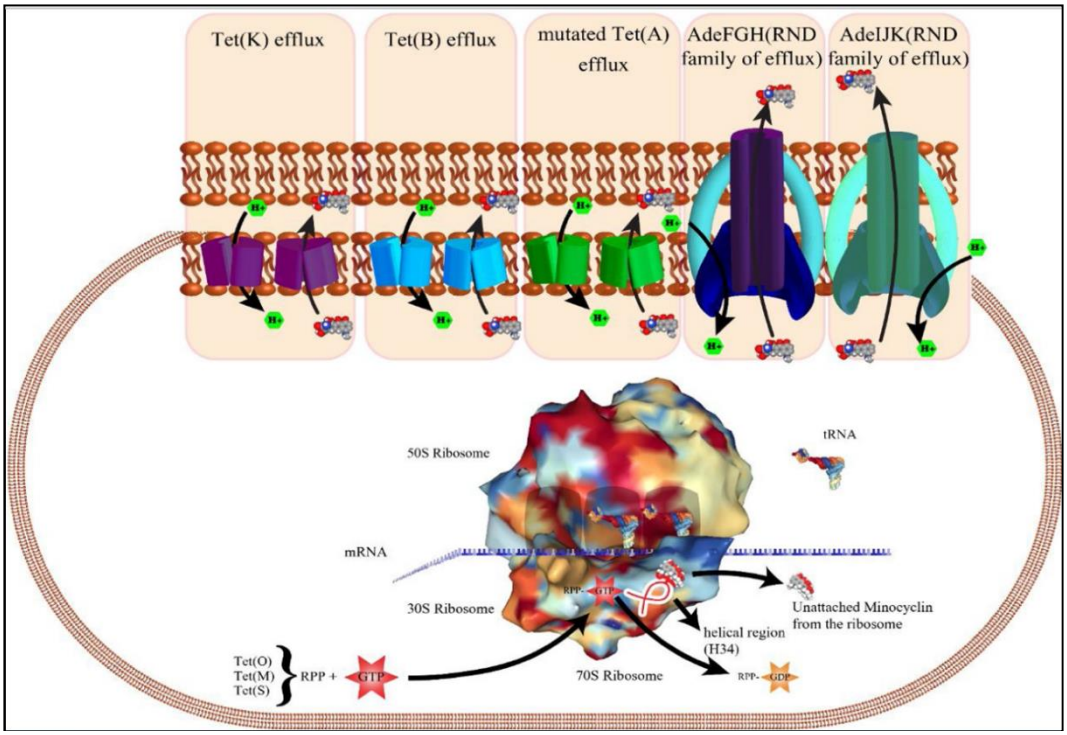


Figure (11): Mechanism of action of Minocycline.

For entry into bacterial cell wall, the minocycline HCl binds to efflux pumps and forms GTP complex (Tet(R)-GTP) complex. The formed complex is attached to a ribosome. GTP molecules get cleaved and then convert to Tet(R)-GDP complex [78]. Then complex gets detached from ribosome and allows it to retain the standard conformation [76]. Minocycline blocks the bacterial process of protein synthesis by avoiding binding with aminoacyl tRNA along with bacterial ribosome. To enrich up to its target, the compound requires to traveling more than one membrane depending upon the

organism, whether it is gram-positive or a gram-negative. Much of the research explains thatthe high affinity of binding site to tetracycline in the 30sribosomal subunit along with protein S7 and 16s rRNA bases involved in binding pocket. Some of the researchers pointed out that, in reality, this evident site is for drug interaction with the ribosome. It cannot reflect proper location and that's why it seems the attachment towards ribosome, which shows high complex changes in 16s rRNA [79]. The minocycline once takes entry into cell, it binds with more concentration of $Mg2^{+}$ ion with the help of C11 and C12 attached oxygen atom. The complex goes to bind with 30s ribosomal subunit and decodes genetic information [80].

Metabolism and Elimination

Minocycline shows different properties from another tetracycline in which it contains a different metabolite in which a minimum of 6 metabolites explains some antimicrobial activity detected in urine. The main metabolite is nothing but the 9-Hydroxyminocycline.Minocycline possesses a delicate half-life of 15-19 hrs., the probability is because of, over-tissue transmission and protein binding of 5-12% of given dose, which retrieved in urine, as well as in fecal elimination. 20-35% of minocycline elimination is unfortunately with the renal or hepatic metabolism. But half-life of drug is highly enhanced in cases with Azotemia [79].

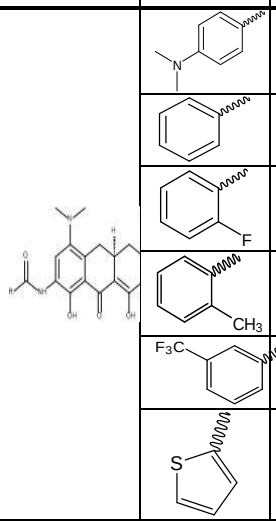
Development of Minocycline derivatives

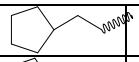
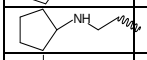
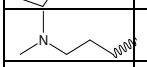
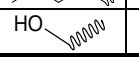
The various minocycline derivatives were synthesized by researchers and tested for their Minimum Inhibitory Concentration (MIC) to the MRSA and gram-positive bacterial strains. The MIC requiredfor minocycline derivatives gives a satisfactory count [81][82][83]. The minocycline shows satisfactory inhibition to MRSA. Hence, the researchersmove ahead to develop new minocycline derivatives to MRSA. The minocycline derivatives are more potent than the standard minocycline drug.

9-Acylamino Derivatives of Minocycline

In minocycline, the 9th Position hydrogen is replaced by the acyl amino group and derivatives are prepared by attaching the various substituents on the amino group. The formed derivatives show the activity to the MRSA with the following MIC [83].

Table (9): 9-Acyclamino derivatives to MRSA with their MIC

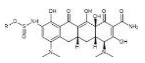
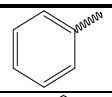
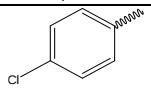
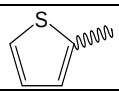
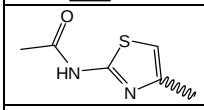
Sr. no.	Parent structure	-R Substituent	MIC (µM)				
			S.aureus UBMS 90-1(tetM)	S. aureusUBMS 90-2 (tetM)	S. aureusUBMS 90-3(sensitive)	S.aureusUBMS88-7(tetK)	S. aureussmith (sensitive)
1.			25.82	12.91	12.91	25.82	6.45
2.			6.93	6.93	1.73	13.88	1.73
3.			6.72	3.25	1.62	13.46	1.62
4.			13.54	3.38	1.69	6.77	1.69
5.			1.55	1.55	0.77	1.55	1.55
6.			6.86	6.86	3.43	54.92	3.43

7.			13.73	13.73	6.86	13.73	6.86
8.			0.39	NT	0.20	3.34	0.42
9.			13.99	6.99	3.49	27.98	3.49
10.			7.74	3.87	1.93	>61.95	0.96

9-Sulfonylamino derivatives of minocycline

In minocycline, the 9th Position hydrogen is replaced by sulphonyl amino group and derivatives are prepared by attaching various substituents on the amino group. The formed derivatives show activity to MRSA with following MIC [83].

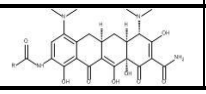
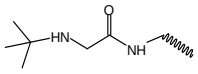
Table (10): 9-Sulphonylamino derivatives to MRSA with their MIC

Sr no	Parent structure	-R Substituent	MIC (µM)				
			S. aureus UBMS 90-1 (tetM)	S. aureus UBMS 90-2 (tetM)	S. aureus UBMS 90-3 (sensitive)	S. aureus UBMS 88-7 (tetK)	S. aureus smith (sensitive)
1.			6.74	0.16	6.74	6.74	6.74
2.			0.39	0.19	0.19	1.59	0.19
3.			1.67	0.41	0.41	3.34	0.005
4.			57.53	6.09	3.04	57.53	3.04
5.			0.47	0.11	0.22	15.07	0.22

9-Glycylcyclines Derivative of minocycline

In minocycline, the 9thposition hydrogen is replaced by glycylcyclinegroup. The formed derivatives show the activity to the MRSA with the following MIC [84].

Table (11): 9-Glycylcyclines derivative to MRSA with its MIC

Sr. no.	Parent structure	-R Substituent	MIC (µM)				
			S. aureus UBMS 90-1 (tetM)	S. aureus UBMS 90-2 (tetM)	S. aureus UBMS 90-3 (sensitive)	S. aureus UBMS 88-7 (tetK)	S. aureus smith (sensitive)
1.			0.79	0.79	0.35	0.35	0.35

Apart from standard drugs, various research has been performed regarding development of new chemical nucleus to MRSA. The bis-thiazolyl pyrazole derivatives shows effective action to MRSA [85]. Thiazolidinonederivatives also have good MIC ranges as well as good docking score to MRSA [86]. Indole-based derivatives show better action to MRSA. It also helps to reduce resistance in MRSA [87]. Designing of truncated derivatives to MRSA [88].Carbazole-oxadiazole derivatives which shows effective action to various gram-positive as well as gram-negative bacteria[89].

Discussion

From the above study, it is clear that the problem starts with various mistakes of humans. The main cause of antibiotic resistance is the false practice of humans. For self-advantage, humans started to use major antibiotics for small infections. And it becomes a severe region for antibiotic resistance. The major issue that occurs nowadays is that various good effective drugs become resistant to different bacteria. The major point of discussion is that if the environment arranges to destroy every living being properly, then man should not interfere with that. Man should not use a major number of fertilizers in agriculture. The industrial waste should be properly disposed. Antibiotics should be used whenever it is only prescribed by doctors. Physicians also do not make an abuse of antibiotics. Otherwise, bacteria continuously mutate themselves and alter gene sequences, to adapt to a new condition. The reason to adopt these practices is that the development of antibiotics is very slow it requires a long-time duration. Because of many reasons, day by day bacteria become too much resistant. Every year mortality counts increase due to resistance of bacteria to various drugs. Because of the development of resistance, many life-threatening infections grab to humans. The standard drugs do not show any effect.Due tothis day by day the rate of mortality due to bacterial infections increases. To overcome this problem, various solution has to be found. Amongst them, one solution can become the use of derivatives for standard drugs. The concept can be counted under the repurposing of drugs. The discovery of newer antibiotics is useful. But till the discovery of newer antibiotics, another way as described in this review can be used. Derivatives of vancomycin, daptomycin, trimethoprim, and linezolid show better effect to resistant bacteria. The dangerous bacterial infection, as mentioned in the section on clinical complications associated with MRSA, can be avoided to a major extent. The development of a greater number of antibiotics can be possible in this way. Many of the medical challenges can be avoided by making availability of various derivatives of the standard drugs. The synthesis of newer derivatives of existing drugs not only helps to avoid antibiotic resistance but also creates a good weapon to fight to bacterial infections. In the future, this concept of repurposing drugs will fight successfully in the war on antibiotic resistance. However, it is possible only when people adopt the practice of not abusing antibiotics. Many of the drug derivatives show potent action to the resistant MRSA. The concentration required to inhibit the growth of the bacteria is also less than the standard drugs. The researchers also have to think in this way of synthesizing new derivatives of standard antibiotics, rather than only focusing on the development of newer drugs. Various in-silico techniques like docking and Molecular Dynamic Simulation (MDS) are also available to speed up the development process. Another aspect for developing new derivatives is to finding out new nucleus which acts as an antibiotic. The government should also focus on that and force the people,especially doctors, to avoid misuse of antibiotics. So, from the above study, it seems that the synthesis of newer derivatives of standard existing drugs can help to avoid antibiotic resistance in MRSA. It gives the ray of hope for saving people's lives from microorganisms, especially from bacteria.

Conclusion

In summary, as per theabove-mentioned study, MRSA become resistant to most of the discovered antibiotics and is susceptible to causing dangerous infections from children to adults. The MRSA becomes resistant due to alteration that occur in the genome sequence of the PBP2a protein. Most antibiotics show no activity to MRSA due to the high expression of resistant genes. But derivatives of existing antibiotic show better effect than the standard drugs. The derivatives of drugs also adopt the same mechanism of action as a standard drug. From MICrequiredto the MRSA as well as gram-positive bacterial strain, the review directs to develop the new derivatives of existing antibiotics until the development of the potent drug. The new derivatives show the effect better than the standard drug and hence the problems created by the MRSA can be restricted by using the newly synthesized derivatives of antibiotics. The process of development of newer antibiotics can be made faster by using this concept of repurposing of drugs.

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Authors contributions

HB and RPB collected and mold the information in the systematic review article. RB had listed out the table. RPB, PB and RC reviewed the article along with conclusions.

Conflict of Interest

The authors declare that no conflicts of interest exist.

Research involving human participants, their data, or biological material require ethical approval

Not applicable.

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Abbreviations

MRSA – Methicillin Resisted *Staphylococcus aureus*

MIC – Minimum Inhibitory Concentration

PBP2a – Penicillin Binding Protein 2a

ICUs – Intentional Care Units

MDR TB – Multi Drug Resistance Tuberculosis

S.aureus– *Staphylococcus aureus*

HA-MRSA - Health Care-Associated Methicillin Resisted *Staphylococcus aureus*

CA-MRSA - Community-Associated Methicillin Resisted *Staphylococcus aureus*

References

1] B. Jubeh, Z. Breijyeh, and R. Karaman, "Resistance of gram-positive-positive bacteria to current antibacterial agents and overcoming approaches," *Molecules*, vol. 25, no. 12, pp. 1–22, 2020, doi: 10.3390/molecules25122888.

2] T. Venkova, C. C. Yeo, and M. Espinosa, "Editorial : The Good , The Bad , and The Ugly : Multiple Roles of Bacteria in Human Life," *Front. Microbiol.*, vol. 9, no. July, pp. 1–4, 2018, doi: 10.3389/fmicb.2018.01702.

3] M. Rohde, "The Gram-positive-positive Bacterial Cell Wall," *Microbiol. Spectr.*, vol. 7, no. May, pp. 1–21, 2019, doi: 10.1128/microbiolspec.GPP3-0044-2018.Correspondence.

4] A. P. Kulkarni *et al.*, "Current Perspectives on Treatment of Gram-positive-positive Infections in India: What Is the Way Forward?," *Interdiscip. Perspect. Infect. Dis.*, vol. 2019, 2019, doi: 10.1155/2019/7601847.

5] S. S. Mohapatra, S. Ranjan, N. (Environmental chemist) Dasgupta, R. K. Mishra, and S. Thomas, *Applications of targeted nano drugs and delivery systems : nanoscience and nanotechnology in drug delivery*.

6] S. L. G. S. Dordon, "Bacterial Infections : Overview," *Elsevier*, no. January, pp. 273–282, 2020.

7] D. G. J. Larsson, "Pollution from drug manufacturing: Review and perspectives," *Philos. Trans. R. Soc. B Biol. Sci.*, vol. 369, no. 1656, 2014, doi: 10.1098/rstb.2013.0571.

8] N. Sabtu, D. A. Enoch, and N. M. Brown, "Antibiotic resistance: What, why, where, when and how?," *Br. Med. Bull.*, vol. 116, no. 1, pp. 105–113, 2015, doi: 10.1093/bmb/ldv041.

9] E. Larson, "Community factors in the development of antibiotic resistance," *Annu. Rev. Public Health*, vol. 28, pp. 435–447, 2007, doi: 10.1146/annurev.publhealth.28.021406.144020.

10] J. Bengtsson-Palme, E. Kristiansson, and D. G. J. Larsson, "Environmental factors influencing the development and spread of antibiotic resistance," *FEMS Microbiol. Rev.*, vol. 42, no. 1, pp.

68–80, 2018, doi: 10.1093/femsre/fux053.
11] A. J. Alanis, "Resistance to antibiotics: Are we in the post-antibiotic era?," *Arch. Med. Res.*, vol. 36, no. 6, pp. 697–705, 2005, doi: 10.1016/j.arcmed.2005.06.009.
12] S. Y. C. Tong, J. S. Davis, E. Eichenberger, T. L. Holland, and V. G. Fowler, "Staphylococcus aureus infections: Epidemiology, pathophysiology, clinical manifestations, and management," *Clin. Microbiol. Rev.*, vol. 28, no. 3, pp. 603–661, 2015, doi: 10.1128/CMR.00134-14.
13] C. T. Walsh, H. Kuhn, B. Chemistry, M. Pharmacology, G. Wright, and B. Sciences, "Introduction : Antibiotic Resistance," vol. 105, no. 2, pp. 391–393, 2005.
14] S. Bin Zaman, M. A. Hussain, R. Nye, V. Mehta, K. T. Mamun, and N. Hossain, "A Review on Antibiotic Resistance: Alarm Bells are Ringing," *Cureus*, vol. 9, no. 6, 2017, doi: 10.7759/cureus.1403.
15] R. L. Finley *et al.*, "The scourge of antibiotic resistance: The important role of the environment," *Clin. Infect. Dis.*, vol. 57, no. 5, pp. 704–710, 2013, doi: 10.1093/cid/cit355.
16] J. Fishovitz, J. A. Hermoso, M. Chang, and S. Mobashery, "Penicillin-binding protein 2a of methicillin-resistant Staphylococcus aureus," *IUBMB Life*, vol. 66, no. 8, pp. 572–577, 2014, doi: 10.1002/iub.1289.
17] T. A. Łęski and A. Tomasz, "Role of penicillin-binding protein 2 (PBP2) in the antibiotic susceptibility and cell wall cross-linking of Staphylococcus aureus: Evidence for the cooperative functioning of PBP2, PBP4, and PBP2A," *J. Bacteriol.*, vol. 187, no. 5, pp. 1815–1824, 2005, doi: 10.1128/JB.187.5.1815-1824.2005.
18] E. E. Ibadin, I. O. Enabulele, and F. Muinah, "Prevalence of mecA gene among staphylococci from clinical samples of a tertiary hospital in Benin city, Nigeria," *Afr. Health Sci.*, vol. 17, no. 4, pp. 1000–1010, 2017, doi: 10.4314/ahs.v17i4.7.
19] E. Carretto, R. Visiello, and P. Nardini, "Methicillin Resistance in Staphylococcus aureus," *Pet-to-Man Travel. Staphylococci A World Prog.*, vol. 85, no. Pt 1, pp. 225–235, 2018, doi: 10.1016/B978-0-12-813547-1.00017-0.
20] K. Hiramatsu *et al.*, "Multi-drug-resistant Staphylococcus aureus and future chemotherapy," *J. Infect. Chemother.*, pp. 1–9, 2014, doi: 10.1016/j.jiac.2014.08.001.
21] Ritesh P. Bhole, Payal M. Karche, Shaliendra S. Gurav, Rupesh V. Chikhale, "Breaking Through Resistance in mCRPC: Enzalutamide analogues as Effective Anticancer Agents for Enhanced Male Survival" ,Results in Chemistry,2023,101143,
22] D. Nakatsuka *et al.*, "[Aortic and mitral valve replacement via right thoracotomy in the case of a patient with severe heart failure following right pneumonectomy]," *Kyobu Geka.*, vol. 67, no. 3, pp. 190–193, 2014, doi: 10.1203/PDR.0b013e31819dc44d.Molecular.
23] R. Maya-Martinez *et al.*, "Recognition of peptidoglycan fragments by the transpeptidase PBP4 from staphylococcus aureus," *Front. Microbiol.*, vol. 10, no. JAN, pp. 1–14, 2019, doi: 10.3389/fmicb.2018.03223.
24] J. A. N. Alexander, S. S. Chatterjee, S. M. Hamilton, L. D. Eltis, H. F. Chambers, and N. C. J. Strynadka, "Structural and kinetic analyses of penicillin-binding protein 4 (PBP4)-mediated antibiotic resistance in Staphylococcus aureus," *J. Biol. Chem.*, vol. 293, no. 51, pp. 19854–19865, 2018, doi: 10.1074/jbc.RA118.004952.
25] P. Sahare and A. Moon, "Penicillin Binding Proteins: An Insight Into Novel Antibacterial Drug Target," *Int. J. Sci. Eng. Res.*, vol. 5, no. 8, pp. 13–23, 2014, [Online]. Available: http://www.ijser.org
26] E. Sauvage, F. Kerff, M. Terrak, J. A. Ayala, and P. Charlier, "The penicillin-binding proteins: Structure and role in peptidoglycan biosynthesis," *FEMS Microbiol. Rev.*, vol. 32, no. 2, pp. 234–258, 2008, doi: 10.1111/j.1574-6976.2008.00105.x.
27] A. Zervosen, E. Sauvage, J. M. Frère, P. Charlier, and A. Luxen, "Development of new drugs for an old target - The penicillin binding proteins," *Molecules*, vol. 17, no. 11, pp. 12478–12505, 2012, doi: 10.3390/molecules171112478.
28] P. Macheboeuf *et al.*, "Structural and mechanistic basis of penicillin-binding protein inhibition by lactivicins," *Nat. Chem. Biol.*, vol. 3, no. 9, pp. 565–569, 2007, doi: 10.1038/nchembio.2007.21.
29] P. D. A. Rohs *et al.*, "A central role for PBP2 in the activation of peptidoglycan polymerization

by the bacterial cell elongation machinery," *PLoS Genet.*, vol. 14, no. 10, pp. 1–25, 2018, doi: 10.1371/journal.pgen.1007726.

30] A. Zapun, C. Contreras-Martel, and T. Vernet, "Penicillin-binding proteins and β-lactam resistance," *FEMS Microbiol. Rev.*, vol. 32, no. 2, pp. 361–385, 2008, doi: 10.1111/j.1574-6976.2007.00095.x.

31] M. Hawash *et al.*, "Molecular docking studies and biological evaluation of isoxazole-carboxamide derivatives as COX inhibitors and antimicrobial agents," *3 Biotech*, vol. 12, no. 12, pp. 1–16, 2022, doi: 10.1007/s13205-022-03408-8.

32] S. Emami, E. Ghafouri, M. Ali, N. Samadi, H. Irannejad, and A. Foroumadi, "European Journal of Medicinal Chemistry Mannich bases of 7-piperazinylquinolones and kojic acid derivatives : Synthesis , in vitro antibacterial activity and in silico study," *Eur. J. Med. Chem.*, vol. 68, pp. 185–191, 2013, doi: 10.1016/j.ejmech.2013.07.032.

33] M. Funovics, X. Montet, F. Reynolds, R. Weissleder, and L. Josephson, "Nanoparticles for the optical imaging of tumor E-selectin," *Neoplasia*, vol. 7, no. 10, pp. 904–911, 2005, doi: 10.1593/neo.05352.

34] F. J. Chen, C. H. Wang, C. Y. Chen, Y. C. Hsu, and K. T. Wang, "Role of the mecA gene in oxacillin resistance in a staphylococcus aureus clinical strain with a pvl-positive ST59 genetic background," *Antimicrob. Agents Chemother.*, vol. 58, no. 2, pp. 1047–1054, 2014, doi: 10.1128/AAC.02045-13.

35] P. Arêde, C. Milheiriço, H. de Lencastre, and D. C. Oliveira, "The anti-repressor MecR2 promotes the proteolysis of the mecA repressor and enables optimal expression of β-lactam resistance in MRSA," *PLoS Pathog.*, vol. 8, no. 7, p. 13, 2012, doi: 10.1371/journal.ppat.1002816.

36] N. A. Turner *et al.*, "Methicillin-resistant Staphylococcus aureus: an overview of basic and clinical research," *Nat. Rev. Microbiol.*, vol. 17, no. 4, pp. 203–218, 2019, doi: 10.1038/s41579-018-0147-4.

37] F. N. Zervou, I. M. Zacharioudakis, P. D. Ziakas, and E. Mylonakis, "MRSA colonization and risk of infection in the neonatal and pediatric icu: A meta-analysis," *Pediatrics*, vol. 133, no. 4, pp. 1014–1023, 2014, doi: 10.1542/peds.2013-3413.

38] B. C. Millar, A. Loughrey, J. S. Elborn, and J. E. Moore, "Proposed definitions of community-associated meticillin-resistant Staphylococcus aureus (CA-MRSA)," *J. Hosp. Infect.*, vol. 67, no. 2, pp. 109–113, 2007, doi: 10.1016/j.jhin.2007.06.003.

39] W. V Kern, "Management of Staphylococcus aureus bacteremia and endocarditis : progresses and challenges," *Lippincott Williams & Wilkins*, vol. 23, no. 4, pp. 346–358, 2010, doi: 10.1097/QCO.0b013e32833bcc8a.

40] R. Rajani and J. L. Klein, "CME: CARDIOVASCULAR MEDICINE Infective endocarditis: A contemporary update," *Clin. Med. (Northfield. Il).*, vol. 20, no. 1, pp. 31–36, 2020.

41] S. Bettencourt and J. M. Ferro, "Acute Ischemic Stroke Treatment in Infective Endocarditis: Systematic Review," *J. Stroke Cerebrovasc. Dis.*, vol. 29, no. 4, 2020, doi: 10.1016/j.jstrokecerebrovasdis.2019.104598.

42] S. A. Hubers, D. C. DeSimone, B. J. Gersh, and N. S. Anavekar, "Infective Endocarditis: A Contemporary Review," *Mayo Clin. Proc.*, vol. 95, no. 5, pp. 982–997, 2020, doi: 10.1016/j.mayocp.2019.12.008.

43] P. Eleonora Widmer, MD, PhD, Yok-Ai Que, MD, PhD, José M. Entenza, PhD, and Philippe Moreillon, MD, "New concepts in the pathophysiology of MS," *Curr. Infect. Dis. Rep.*, no. 8, pp. 271–279, 2006.

44] L. B. Pereira, "Impetigo - Review," *An. Bras. Dermatol.*, vol. 89, no. 2, pp. 293–299, 2014, doi: 10.1590/abd1806-4841.20142283.

45] Z. Lior, C. Lior, and C. Gideon, "Current Microbiological, Clinical and Therapeutic Aspects of Impetigo," *Clin. Med. Rev. Case Reports*, vol. 5, no. 2, pp. 1–9, 2018, doi: 10.23937/2378-3656/1410205.

46] L. Miguel-Gómez, D. Saceda-Corralo, R. Rodrigues-Barata, and S. Vañó-Galván, "Folliculitis Decalvans," *Alopecia*, vol. 21, no. 15, pp. 161–165, 2018, doi: 10.1016/B978-0-323-54825-0.00014-4.

47] P. Bloom, "Canine superficial bacterial folliculitis: Current understanding of its etiology, diagnosis and treatment," *Vet. J.*, vol. 199, no. 2, pp. 217–222, 2014, doi: 10.1016/j.tvjl.2013.11.014.
48] J. A. Silversides, E. Lappin, and A. J. Ferguson, "Staphylococcal toxic shock syndrome: Mechanisms and management," *Curr. Infect. Dis. Rep.*, vol. 12, no. 5, pp. 392–400, 2010, doi: 10.1007/s11908-010-0119-y.
49] I. G. *et al.*, "Primary Staphylococcus aureus urinary tract infection: The role of undetected hematogenous seeding of the urinary tract," *Eur. J. Clin. Microbiol. Infect. Dis.*, vol. 29, no. 9, pp. 1095–1101, 2010, doi: 10.1007/s10096-010-0967-2.
50] S. Amrith, V. Hosdurga Pai, and W. W. Ling, "Periorbital necrotizing fasciitis - A review," *Acta Ophthalmol.*, vol. 91, no. 7, pp. 596–603, 2013, doi: 10.1111/j.1755-3768.2012.02420.x.
51] C. Ngor, L. Hall, J. A. Dean, and C. F. Gilks, "Factors associated with pyomyositis: A systematic review and meta-analysis," *Trop. Med. Int. Heal.*, vol. 26, no. 10, pp. 1210–1219, 2021, doi: 10.1111/tmi.13669.
52] N. Chatha, D. Fortin, and K. J. Bosma, "Management of necrotizing pneumonia and pulmonary gangrene: A case series and review of the literature," *Can. Respir. J.*, vol. 21, no. 4, pp. 239–245, 2014, doi: 10.1155/2014/864159.
53] J. L. Marsh, P. A. Watson, and C. A. Crouch, "Septic arthritis caused by chronic osteomyelitis.," *Iowa Orthop. J.*, vol. 17, pp. 90–95, 1997.
54] B. Gyawali, K. Ramakrishna, and A. S. Dhamoon, "Sepsis : The evolution in definition , pathophysiology , and management," *SAGE Open Med.*, vol. 7, pp. 1–13, 2019, doi: 10.1177/2050312119835043.
55] E. J. Choo and H. F. Chambers, "Treatment of methicillin-resistant Staphylococcus aureus bacteremia," *Infect. Chemother.*, vol. 48, no. 4, pp. 267–273, 2016, doi: 10.3947/ic.2016.48.4.267.
56] G. L. French, "Bactericidal agents in the treatment of MRSA infections - The potential role of daptomycin," *J. Antimicrob. Chemother.*, vol. 58, no. 6, pp. 1107–1117, 2006, doi: 10.1093/jac/dkl393.
57] M. Hasannejad-Bibalan, A. Mojtahedi, H. Biglari, M. Halaji, and H. Sedigh Ebrahim-Saraie, "Antibacterial Activity of Tedizolid, a Novel Oxazolidinone to Methicillin-Resistant Staphylococcus aureus: A Systematic Review and Meta-Analysis," *Microb. Drug Resist.*, vol. 25, no. 9, pp. 1330–1337, 2019, doi: 10.1089/mdr.2018.0457.
58] S. Kumar Verma, R. Verma, F. Xue, P. Kumar Thakur, Y. R. Girish, and K. P. Rakesh, "Antibacterial activities of sulfonyl or sulfonamide containing heterocyclic derivatives and its structure-activity relationships (SAR) studies: A critical review," *Bioorg. Chem.*, vol. 105, p. 104400, 2020, doi: 10.1016/j.bioorg.2020.104400.
59] A. S. Rao and K. Road, "A STUDY ON DIHYDROFOLATE REDUCTASE AND ITS INHIBITORS: A REVIEW A.S. Rao* and S. R. Tapale AISSMS College of Pharmacy, Kennedy Road, Near RTO Office, Pune- 411 041, Maharashtra, India," *Int. J*, vol. 4, no. 7, pp. 2535–2547, 2013, doi: 10.13040/IJPSR.0975-8232.4(7).2535-47.
60] N. M. Haste *et al.*, "Activity of the streptogram-positivein antibiotic etamycin to methicillin-resistant Staphylococcus aureus," *J. Antibiot. (Tokyo).*, vol. 63, no. 5, pp. 219–224, 2010, doi: 10.1038/ja.2010.22.
61] S. Vandendriessche, K. Kadlec, S. Schwarz, and O. Denis, "Methicillin-susceptible Staphylococcus aureus ST398-t571 harbouring the macrolide-lincosamide-streptogram-positivein B resistance gene erm(T) in Belgian hospitals," *J. Antimicrob. Chemother.*, vol. 66, no. 11, pp. 2455–2459, 2011, doi: 10.1093/jac/dkr348.
62] Y. Hirai *et al.*, "Characterization of compound A, a novel lincomycin derivative active to methicillin-resistant Staphylococcus aureus," *J. Antibiot. (Tokyo).*, vol. 74, no. 2, pp. 124–132, 2021, doi: 10.1038/s41429-020-00375-1.
63] L. R. Peterson, "A review of tigecycline - the first glycylcycline," *Int. J. Antimicrob. Agents*, vol. 32, no. SUPPL. 4, pp. S215–S222, 2008, doi: 10.1016/S0924-8579(09)70005-6.
64] K. Bush and P. A. Bradford, "Bush and Bradford - 2016 - β-Lactams and β-Lactamase Inhibitors An Overview.pdf," *Cold Spring Harb. Perspect. Meddicine*, no. Table 1, p. 22, 2016.

65] J. A. Roberts, S. Webb, D. Paterson, K. M. Ho, and J. Lipman, "A systematic review on clinical benefits of continuous administration of β-lactam antibiotics," *Crit. Care Med.*, vol. 37, no. 6, pp. 2071–2078, 2009, doi: 10.1097/CCM.0b013e3181a0054d.

66] S. Jovetic, Y. Zhu, G. L. Marcone, F. Marinelli, and J. Tramper, "β-Lactam and glycopeptide antibiotics: First and last line of defense?," *Trends Biotechnol.*, vol. 28, no. 12, pp. 596–604, 2010, doi: 10.1016/j.tibtech.2010.09.004.

67] Y. Hu *et al.*, "Combinations of β-lactam or aminoglycoside antibiotics with plectasin are synergistic to methicillin-sensitive and methicillin-resistant Staphylococcus aureus," *PLoS One*, vol. 10, no. 2, pp. 1–15, 2015, doi: 10.1371/journal.pone.0117664.

68] A. Dhand and G. Sakoulas, "Daptomycin in combination with other antibiotics for the treatment of complicated Methicillin-resistant staphylococcus aureus bacteremia," *Clin. Ther.*, vol. 36, no. 10, pp. 1303–1316, 2014, doi: 10.1016/j.clinthera.2014.09.005.

69] W. T. Liu *et al.*, "Emerging resistance mechanisms for 4 types of common anti-MRSA antibiotics in Staphylococcus aureus: A comprehensive review," *Microb. Pathog.*, vol. 156, no. April, p. 104915, 2021, doi: 10.1016/j.micpath.2021.104915.

70] M. R. Leadbetter *et al.*, "Hydrophobic vancomycin derivatives with improved ADME properties: Discovery of telavancin (TD-6424)," *J. Antibiot. (Tokyo).*, vol. 57, no. 5, pp. 326–336, 2004, doi: 10.7164/antibiotics.57.326.

71] M. P. and S. D. T. Ghufran Barnawi, Michael Noden, Jeremy Goodyear, Julian Marlyn, Olivia Schneide, David Beriashvili, Sarah Schulz, Ryan Moreira, "Discovery of Highly Active Derivatives of Daptomycin by Assessing the Effect of Amino Acid Substitutions at Positions 8 and 11 on a Daptomycin Analogue," *ACS Infect. Dis.*, vol. 8, no. 4, pp. 778–789, 2022, doi: https://doi.org/10.1021/acsinfecdis.1c00483.

72] Y. Hou *et al.*, "Synthesis and antibacterial evaluation of novel oxazolidinone derivatives containing a piperidinyl moiety," *Bioorganic Med. Chem. Lett.*, vol. 29, no. 23, p. 126746, 2019, doi: 10.1016/j.bmcl.2019.126746.

73] M. Krátký, J. Vinšová, M. Volková, V. Buchta, F. Trejtnar, and J. Stolaříková, "Antimicrobial activity of sulfonamides containing 5-chloro-2- hydroxybenzaldehyde and 5-chloro-2-hydroxybenzoic acid scaffold," *Eur. J. Med. Chem.*, vol. 50, pp. 433–440, 2012, doi: 10.1016/j.ejmech.2012.01.060.

74] N. Nilchan, W. Phetsang, T. Nowwarat, S. Chaturongakul, and C. Jiarpinitnun, "Halogenated trimethoprim derivatives as multidrug-resistant Staphylococcus aureus therapeutics," *Bioorganic Med. Chem.*, vol. 26, no. 19, pp. 5343–5348, 2018, doi: 10.1016/j.bmc.2018.05.019.

75] N. Garrido-Mesa, A. Zarzuelo, and J. Gálvez, "Minocycline: Far beyond an antibiotic," *Br. J. Pharmacol.*, vol. 169, no. 2, pp. 337–352, 2013, doi: 10.1111/bph.12139.

76] A. Asadi *et al.*, "Minocycline, focus on mechanisms of resistance, antibacterial activity, and clinical effectiveness: Back to the future," *J. Glob. Antimicrob. Resist.*, vol. 22, pp. 161–174, 2020, doi: 10.1016/j.jgar.2020.01.022.

77] S. F. Askari Rizvi, "Tetracycline: Classification, Structure Activity Relationship and Mechanism of Action as a Theranostic Agent for Infectious Lesions-A Mini Review," *Biomed. J. Sci. Tech. Res.*, vol. 7, no. 2, pp. 5787–5796, 2018, doi: 10.26717/bjstr.2018.07.001475.

78] M. D. Routh, C. C. Su, Q. Zhang, and E. W. Yu, "Structures of AcrR and CmeR: Insight into the mechanisms of transcriptional repression and multi-drug recognition in the TetR family of regulators," *Biochim. Biophys. Acta - Proteins Proteomics*, vol. 1794, no. 5, pp. 844–851, 2009, doi: 10.1016/j.bbapap.2008.12.001.

79] E. Bishburg and K. Bishburg, "Minocycline-an old drug for a new century: emphasis on methicillin-resistant Staphylococcus aureus (MRSA) and Acinetobacter baumannii," *Int. J. Antimicrob. Agents*, vol. 34, no. 5, pp. 395–401, 2009, doi: 10.1016/j.ijantimicag.2009.06.021.

80] W. Guerra, P. P. Silva-Caldeira, H. Terenzi, and E. C. Pereira-Maia, "Impact of metal coordination on the antibiotic and non-antibiotic activities of tetracycline-based drugs," *Coord. Chem. Rev.*, vol. 327–328, pp. 188–199, 2016, doi: 10.1016/j.ccr.2016.04.009.

81] D. C. Draghi, S. Tench, M. J. Dowzicky, and D. F. Sahm, "Baseline in vitro activity of tigecycline among key bacterial pathogens exhibiting multidrug resistance," *Chemotherapy*, vol. 54, no. 2, pp. 91–100, 2008, doi: 10.1159/000118660.

82] D. J. Hoban, S. K. Bouchillon, B. M. Johnson, J. L. Johnson, and M. J. Dowzicky, "In vitro activity of tigecycline to 6792 Gram-positive-negative and Gram-positive-positive clinical isolates from the global Tigecycline Evaluation and Surveillance Trial (TEST Program-positive, 2004)," *Diagn. Microbiol. Infect. Dis.*, vol. 52, no. 3, pp. 215–227, 2005, doi: 10.1016/j.diagmicrobio.2005.06.001.

83] K. B. Waites, L. B. Duffy, and M. J. Dowzicky, "Antimicrobial susceptibility among pathogens collected from hospitalized patients in the United States and in vitro activity of tigecycline, a new glycylcycline antimicrobial," *Antimicrob. Agents Chemother.*, vol. 50, no. 10, pp. 3479–3484, 2006, doi: 10.1128/AAC.00210-06.

84] P. E. Sum, A. T. Ross, P. J. Petersen, and R. T. Testa, "Synthesis and antibacterial activity of 9-substituted minocycline derivatives," *Bioorganic Med. Chem. Lett.*, vol. 16, no. 2, pp. 400–403, 2006, doi: 10.1016/j.bmcl.2005.09.078.

85] S. A. Ibrahim, E. A. Fayed, H. F. Rizk, S. E. Desouky, and A. Ragab, "Hydrazonoyl bromide precursors as DHFR inhibitors for the synthesis of bis-thiazolyl pyrazole derivatives; antimicrobial activities, antibiofilm, and drug combination studies to MRSA," *Bioorg. Chem.*, vol. 116, no. September, p. 105339, 2021, doi: 10.1016/j.bioorg.2021.105339.

86] B. P. Vasantha Kumar, Premalatha Shetty, Arunodaya H. S., Sharath Chandra K., Ramith Ramu, Shashank M. Patil, Anuradha Baliga, Vaishali M. Rai, Shalini Shenoy M, Vishwanatha Udupi, Vishwanatha Poojary, "Potential Fluorinated Anti-MRSA Thiazolidinone Derivatives with Antibacterial, Antitubercular Activity and Molecular Docking Studies," *Chem. Biodivers.*, 2021, doi: https://doi.org/10.1002/cbdv.202100532.

87] H. L. Qin, J. Liu, W. Y. Fang, L. Ravindar, and K. P. Rakesh, "Indole-based derivatives as potential antibacterial activity to methicillin-resistance Staphylococcus aureus (MRSA)," *Eur. J. Med. Chem.*, vol. 194, p. 112245, 2020, doi: 10.1016/j.ejmech.2020.112245.

88] Y. Ma *et al.*, "Generation of truncated derivatives through in silico enzymatic digest of peptide GV30 target MRSA both in vitro and in vivo," *Comput. Struct. Biotechnol. J.*, vol. 19, pp. 4984–4996, 2021, doi: 10.1016/j.csbj.2021.08.039.

89] C.H. Z. Yun-Peng Xie, Nagarajan Sangaraiah, Jiang-Ping Meng, "Unique Carbazole-Oxadiazole Derivatives as New Potential Antibiotics for Combating Gram-positive-positive and -Negative Bacteria," *J. Med. Chem.*, vol. 65, no. 8, pp. 6171–6190, 2022, doi: https://doi.org/10.1021/acs.jmedchem.2c00001.