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A Review on Resistance of Antibiotics against Methicillin-Resistant *Staphylococcus aureus* and effect of Curcumin on MRSA

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Abstract

Antibiotics were ceaselessly used to treat bacterial infections and their constant use has developed high degree of resistance in bacteria. Methicillin-resistant *staphylococcus aureus* (MRSA) is one among such potent bacteria that has been a great concern in almost all areas of medicine. They almost halted the golden era of antibiotics. MRSA has been the reason for most of community acquired infections and hospital acquired infections. The presence of a mutant in the bacteria makes it resistant against most of the antibiotics. Because of the lack of treatment and expanded death rate there is a requirement for a potent therapy to convey an end to this bacterial infection.

Key Words- Curcumin, MRSA, Penicillin binding protein, *Staphylococcus aureus*, β-lactam antibiotics

INTRODUCTION

Methicillin-resistant *Staphylococcus aureus* is a gram positive bacteria and an antibiotic resistant strain of *staphylococcus aureus*. It has been found to be one of the reasons for nosocomial infections. In 1972 it was from mastitic infected cattle MRSA was first isolated. Animals and humans are mostly infected by these bacteria. The infections include rashes, oesteomyelitus, septicaemia and pneumonia [1]. This strain of S.*aureus* has become a worldwide threat due to lack of treatment against this bacteria. National nosocomial infection surveillance system shows that S.*aureus* is the most common cause for nosocomial pneumonia and one of the causes for bloodstream infections in USA. In USA the mortality rate of different diseases like AIDS, MRSA infection, hepatitis and tuberculosis were compared and interestingly it was found that the mortality rate was found to be more for MRSA infections. The prevalence rate for MRSA infections in developed countries were found to be: UK (44%), Japan (60-70%), USA (>50%) [2]. But 2011 reports shows that the mortality rate in USA has declined due to proper hospital care management. The bacterium is resistant to β- lactam antibiotics like penicillin, methicillin, erythromycin etc. Their resistance to antibiotics is due to the presence of mecA and mecC gene. MecA gene plays a major role in the production of penicillin binding protein 2a (PBP2a) [2]. PBPs are membrane bound enzymes that helps in catalyzation of transpeptide reaction which is needed for the cross-linkage of peptidoglycan chains. Due to low affinity of PBPs to β-lactam antibiotics, *Staphylococcus aureus* can withstand high concentrations of these antibiotics [3]. In some MRSA strains the resistance is mainly influenced by a group of genes called 'blaz'. Another series of genes known as fem genes also plays an essential role in resistance to methicillin by cross linking peptidoglycan strands. The recent studies shows that the MRSA were resistant towards methicillin (45.9%), cefixame (44%), co-trimoxazole (28%), erthyromycin (28%), gentamycin (18%). But 100% were sensitive to vancomycin (glycopeptide) [2]. Need of discovery for new antibiotics become important when vancomycin resistant MRSA was isolated in 1996 from Japan [1]. Linezolid is one of the synthetic antibiotics used recently for the treatment. They act by destroying the bacterial growth by inhibiting the initiation process in protein synthesis. Linezolid also helps in inhibiting virulence factor expression and reduces the amount of poison produced by gram positive pathogens. Studies have shown that drugs against MRSA should be protein synthesis inhibitors with a gram positive spectrum, eg: quinupristin, dalfopristin [4]. Studies have shown that MRSA has been acquired from hospital care workers who have poor handwashing techinques. So these conditions can be minimised by improving hand washing techniques. MRSA can be controlled by identifying their colonies or the persons who are infected by it. Active Detection and Isolation (ADI) (which include screening high risk patients for MRSA, taking precaution for those who are MRSA positive, adopting proper hand hygiene techniques) can be used as a controlling technique for MRSA infections [5].

ANTIBIOTIC ACTION

The discovery of penicillin by Alexander Fleming opened the door for other antibiotics to the world. Antibiotic used to treat various diseases has specific site for its action [3]. In the recent world majority of diseases has been cured with the antibiotics, this lead to the detailed study about this class of drugs. They are classified on the basis of mechanism of action, chemical structure, or spectrum of activity. They act by inhibiting cell growth leading to lysis of cell. Classification on the basis of mechanism of action as follows:

Cell wall growth inhibitors

The following class of drugs acts by this mechanism: β-lactam antibiotics, glycopeptides, bacitracin

a) β-lactam antibiotics

Eg: pencillins and cephalosporins

mechanism of action:

Major component of cell wall comprises of peptidoglycans [6]. The peptidoglycans are made of N-acetyl glucosamine and N-acetyl muramic acid. The n-acetyl muramic acid unit contains peptide chains which are the site of crosslinking. The S.*aureus* contains pentapeptide chains of L-Ala-γ-D-Glu-L-Lys (Gly) 5-D-Ala-D-Ala [7]. These are produced within the cell but the cross linking takes place outside the cell. The cross linking is done by a group of enzymes known as transpeptidases. These classes of Enzymes are called Penicillin Binding Proteins (PBP).These are bifunctional enzymes having both transpeptidase domain and transglycosylase domain. The transglycosylase domain of the enzyme helps in the extension of the sugar by the addition of new peptidioglycan units from N-acetylglucosamine-b-1, 4-*N*-acetylmuramyl-pentapeptide-pyrophosphoryl-undecaprenol [6]. The transpeptidases perform their activity by acylation using serine as their active site [8]. The β-lactam antibiotics act on these enzymes. They form covalent pencilloyl complex which prevents the cross linking reactions and their by inhibiting the cell wall synthesis.

b) glycopeptides

E.g : vancomycin,

Mechanism of action: It targets D-Ala-D-Ala terminal of cell wall (peptidoglycan chain) inhibiting the transpeptidase activity. Thus they prevent the cross linking of peptidoglycans which results in poor cell wall synthesis. The resistance can arise by increasing the thickness of cell wall. Vancomycin binds to the D-ala-D-ala

terminal through five hydrogen bonds. This results in high affinity of antibiotics to its target but production of D-ala-D-lac lead to resistance against the site.

c) bicitracin

They interfere with dephosphorylation of C_{55}-isoprenyl pyrophosphate which is a membrane carrier molecule that transports the building blocks of bacterial cell wall [9]. It also acts as a receptor in plasma membrane of bacteria.

NATURE OF RESISTANCE

Wide spread of MRSA has made an interest on identifying the mechanism of resistance of S.*aureus* against different antibiotics. It has been reported that most of the antibiotics used to treat MRSA have acquired resistance against its action. β– lactam antibiotics which have greater onset of action against the infection and so this class of drugs (penicillin, erythromycin) was used. Methicillin is no longer used due to its nephrotoxicity, yet the *Staphylococcus aureus* resistant to cloxacillin or nafcillin are refered as methicillin resistant organism. The action of β–lactam antibiotics is due to the presence of Penicillin Binding Protein (PBP) in the cell wall of bacteria which have affinity over β–lactam antibiotics covalently [8]. The key role of β–lactam antibiotics is that it acts as substrate analogues for PBPs which helps in catalyzing transpeptidation. Most commonly the resistance is introduced by the production of enzymes which alters the antibiotic structure [10]. Most of the clinically obtained MRSA contain a staphylococcal origin gene mecA coding 78kd PBP2a having affinity towards β-lactam ring [11]. General assumption has made that mecA gene act as surrogate enzyme for synthesis of cell wall. MecA gene have structural resemblance of cell wall synthesizing transpeptidase. This mecA gene can easily transfer fron one to other S. aureus [12]. A bacterial cell wall is composed of repeating units of disaccharides which include N-acetyl glucosamine and N- acetyl muramic acid. The N-acetyl muramic acid is modified by pentapeptides which is one of the differentiating factor in gram positive and gram negative bacteria. The peptidoglycan is produced inside the cell but their crosslinking takes place outside the cell membrane. Transpeptidases are the enzymes which does this function. After the cross-linking a peptide bond is formed between D-alanine group of one chain with the L-lysine group of the other. Transpeptidases enzyme uses an active serine and performs their function by acylation. This is the site where β-lactam antibiotics act to produce their effect. They inhibit the transpeptidases enzyme thereby preventing the cross-linking of peptidoglycans. The transpeptidase enzyme forms a strong covalent bond with the antibiotics and thereby prevents the further reactions. Since the S.*aureus* has attained resistance over this mechanism mecA gene takes over the step of cell wall synthesis. This leads to the investigation for other site to fight against the resistance.

MECHANISM OF RESISTANCE

The bacterial cells produce resistance against antibiotics by three mechanisms:

- Preventing the antibiotic attack to the target site by mechanism of altered permeability(via efflux pumps)
- By transforming the target site
- By the inactivation of antibiotics (by enzymes) [13]

1. Enzymatic action:

The β-lactamses classes of enzymes are responsible for this activity. They are also called as pencillinase or cephalosporinase. Penicillinase is mostly active against penicillin whereas cephalosporinase are active against cephalosporins. Sometimes both types are present in the same organism. It is one of the defense mechanism against antibiotics in gram negative bacteria. β-lactamases cleaves the β-lactam ring of pencillin and other antibiotics [3]. They are classified into four classes (A to D). They all have mechanism that involves the nucleopilic attack of β-lactam antibiotics on the active site serine which results in acyl-enzyme intermediate [8]. This is a type of nucleophilic substitution reaction in which β-lactam ring act as a nucleophile. This intermediate is hydrolyzed by base activated water molecule. Generally β-lactamases inhibitors are given in combination with β-lactam antibiotics to counteract this resistance.

Extended spectrum β-lactamases (ESBLs) intercede protection from all pencillins, third generation cephalosporins. They are for the most part distinguished in E.coli yet additionally have been found in enterobacteriaceae. [13]

2. Target alteration:

The second mechanism includes target modification so that the antibiotic can't bind legitimately. Due to the imperative cell elements of the objective locales, creatures can't sidestep antimicrobial activity by abstaining from them completely. Generally the target for β-lactam antibiotics is to inhibit cell wall synthesis. This is achieved by their capacity to bind covalently with radiolabelled penicillin. These proteins to which antibiotics (β-lactam antibiotics) bind are called Pencillin Binding Protein (PBP). A given life form contains four to eight PBPs with sub-atomic sizes of 35 to 120 kDa. There is no fundamental connection between identically numbered PBPs of two random organisms, although taxonomically related organisms have comparable PBPs. There are two types of PBPs in an organism based on their molecular weight- Low molecular weight and high molecular weight PBP [14]. Most of the microorganisms are resistant to penicillins because of the alteration of PBPs. This alteration mostly occurs due to procured mutation or due to any chromosomal facto r exchange. Resistance to macrolides is due to the attainment of one of 21 erm genes. These genes codes for rRNA methylases which are the enzymes for the addition of a methyl group on adenine residues in 23s rRNA. These inhibits the binding of macrolides to 50s ribosomal subunit [5]. PBP2a belong to the class of high molecular weight PBPs. Most of the PBPs have high transpeptidase activity which is required for the crosslinking of membranes proteins. This transpeptidase activity of PBPS has been inhibited by methicillin but they were not able to inhibit PBP2a because they largely depend on transglycosylase activity.

PBP2a is encoded by a mecA gene which is present at the 30kb DNA segment. These are present in the chromosome of MRSA. This is an additional gene present in MRSA which are found to be absent in MSSA (methicillin susceptible *Staphylococcus aureus*). Vancomycin was one of the important drugs which were used for the treatment against MRSA infections, but unfortunately in the last few years MRSA has acquired resistance against vancomycin. This is due to presence of van A which caused alteration in the vancomycin binding site. It is accompanied with three fold increase in the production PBP2a and PBP2'. Similarly most of the drugs including oxacillin became ineffective due to the presence of PBP2a [4]. Their major fuction is to provide the transpeptidase and transglycosylase activity which are important for the cross-linking of cell wall. These are inhibited by β-lactam antibiotics in susceptible species.

The other target alterations include alteration in protein synthesis, alteration DNA synthesis. The mechanism of action of macrolides and lincosamide is different from that of β-lactam antibiotics. They inhibit the protein synthesis by binding with 50s ribosomal subunit. But MRSA shows resistance toward macrolides and lincosamide by the alteration in 23s ribosomal component of 50s ribosomal subunit. These occurs during the post transcriptional period where the 23s rRNA component get altered and therefore the macrolides cannot bind to the 50s subunit. The drugs which act by inhibiting the dna replication and transcription are the quinolines especially fluoroquiolines. They mainly inhibit the dna

gyrase and topoisomerase enzymes. The resisitance to quinolines in mrsa occurs by mutation in the structural gene which alters both the enzymes. This reduces the affinity of enzymes to quinolines [3].

3. preventing the antibiotic attack to the target site (efflux pumps)

A drug has to reach its specific target to produce its therapeutic action. Drug resistance can be acquired by preventing the antibiotic from reaching its target site. This can be achieved by means of efflux pumps. Efflux pumps are membrane proteins that export antibiotics out of the cell. A drug concentration inside the cell depends on its permeability through the cell membrane. Resistance to penicillin in gram negative bacteria occurs mainly by this mechanism. The outer membrane of bacteria contains aqueous channels formed by proteins called porins which allows the rapid entry of most of the antibiotics. Mutations in the gene coding for porins can prevent the entry antibiotics into the cell. Efflux pumps are one of the important systems which are involved in the expulsion of tetracycline from the cell [14]. It is one of the most identified and studied mechanism by which tetracycline resistance is caused. The tetracycline accumulation in bacteria is related with energy supplied in the cell. The studies have shown that tetracycline expelled out of the cell in presence of energy and its accumulation increases when energy is not supplied. This was carried out by specific proteins present in the outer membrane called tet protein. The efflux system by the tet protein is indeed a antiport system which export one molecule of tetracycline out of the cell for one proton which is entering into the cell. Efflux pumps may be of single or multi component pumps. The presence of multi drug efflux pumps is the reason for multi-drug resistance in most of the bacteria. Efflux pumps are regulated by specific genes which can themselves be a target for the antibacterial agents. They are mostly regulated by global receptors which include marA, soxS, rob. They are also regulated by two component system. Any mutations in these genes can reduce the resistance and therefore it increases the susceptibility of organisms to antibiotics. Efflux inhibitors can be used for this purpose [13].

ANTI-BACTERIAL EFFECT OF CURCUMIN AGAINST METHICILLIN RESSISTANT STAPHYLOCOCCUS AUREUS

MRSA (Methicillin-Resistant *Staphylococcus aureus*) is a rapidly spreading infectious disease and their ability of high resistance to antibiotics lead to some serious provocations regarding the treatment of this disease [15]. *Curcuma longa* a herbaceous rhizome have many actions in human body. It is native to India and south Asian countries. Major constituent curcumin has several properties like anti-bacterial, anti-inflammatory, antioxidant and anti-amyloid activities [16]. It has less repercussion in pregnancy and lactation period [17]. The major constituent curcumin has exhibited a wide range of pharmacological action at low doses [18]. At higher doses curcumin shows genotoxicity. Curcumin is extracted from turmeric by solvent extraction with the help of various methods such as Soxhlet, microwave etc [18]. Curcumins antibacterial activity was tested against the strains of MRSA by combining with other antibiotics such as oxacillin, ampicillin and norfloxacin showed positive results by reducing the minimum inhibitory concentration of the drug thus reducing the bacterial count to a high extent [15]. A standard broth micro dilution method was used here. Curcumin were prepared in MHB in sterile conditions [15]. A checker board test was done to evaluate two or more drug combinations and respective assays were performed with OXI, AMP, CIP and NOR. Interactions between the in vitro drugs were determined by the fractional inhibitory concentration or (FIC) index [15].

FIC index = FICa + FICb = [A]/MICa + [B]/MICb where,
[A]=CONCENTRATION OF DRUG A
[B]=CONCENTRATION OF DRUG B

FIC and MIC are the respected minimum inhibitory concentratiom values for drugs A and B [15]. In a research MIC calculated through computational studies shows that curcumin conjugated chitosan microspheres has more action against S. aureus than curcumin alone [19].

The cheker board broth method provided more precise results and suitable for studies with multiple concentration of compounds. The main mechanism behind curcumin is able to reverse the resistance when used in combination with other drugs [18].

Disadvantage of curcumins

There are also certain things which challenge the use of curcumin as an antibiotic which mainly include evidences of cytotoxcicity. Another one includes the ability to promote lung cancer. It is linked to the induction of reactive oxygen species (ROS) such as hydrogen peroxide [18]. Nausea, diarrhea and increased serum alkaline phosphatase are one of the major after impact. In addition to this curcumin has poor solubility and low bioavailability due to rapid metabolism by sulphation, methylation and glucaronidation [20]. In presence of detoxifying enzymes curcumin will get degraded rapidly. But studies have also shown that the products obtained from degradation of curcumin is mainly responsible for the pharmacological actions [18]. Curcumin treatment may cause growths despite the anticancer activity of curcumin is very much archived. As curcumin is an effective iron chelator, it might conceivably influence fundamental iron digestion particularly the individuals who have problematic iron status. Moreover curcumin has been accounted for to hinder the compounds that use medications, such as cytochrome p450s. This may prompt the aggregation of non metabolized medicates in blood and ends up causing toxicity [18]. Notwithstanding potential danger, poor solvency, and low boo availability, curcumin experiences several difficulties when it is regulated either through oral or intra venous course because of the idea of body frame work. A lot of curcumin may get corrupted within the sight of detoxifying and metabolic compounds, or it might tie to the circulatory proteins, for example, egg white which may possibly diminish its action [18].

Resistance

Curcumin has demonstrated powerful antibacterial action and other pharmacological activities in the past few years [15]. Curcumin has been showcased all around as a well being supplement essential for its cell reinforcements and calming properties. Likewise, it additionally can possibly be created into a anti-toxin against Methicillin-Resistant *Staphylococcus Aureus* and other bacterial strains later on.

ANTIBIOTIC COMBINATIONS AGAINST MRSA

Methicillin-Resistant *Staphylococcus aureus* (MRSA) is a considerable general medical issue around the world, causing huge dreariness and mortality and raised medicinal services costs. There were an expected 94360 obtrusive MRSA contaminations in the United States in 2005, causing more than 18 000 passing's for every year. Methicillin-Resistant S. *aureus* pervasiveness has expanded in the course of the most recent 10 years; MRSA-related doctor's facility releases have multiplied more than 10 years, with doctor's facility releases for MRSA skin and delicate tissue contamination tripling since 2004.Infections caused by MRSA are related with longer healing center stays and an expanded budgetary weight on society, costing an expected US $14.5 billion for all inpatient days in 2003.An case of the expanded grimness and mortality related with MRSA can be seen when contrasting the yearly disease rates and death rates in the United States for MRSA, AIDS, viral hepatitis, and tuberculosis. Methicillin-

Resistant S aureus is evaluated to cause a larger number of contaminations than alternate maladies consolidated and a bigger number of passings every year than AIDS [1].

B- **LACTAM BINDING ACTION, A DETAILED STUDY**

A vast assortment of anti-microbial blends are of now being used against MRSA contaminations the vast majority of the anti-microbial mixes act synergically and is bactericidal against MRSA. Drugs, for example, vancomycin and linezolid are the most broadly utilized. Twofold blends, for example, vancomycin with imipenem and fosfomycin with cetazolin were utilized however wound up as disappointments. Most antimicrobial operators utilized for the treatment of bacterial contaminations might be sorted concurring their important system of activity. There are four major route of actions [3]. (1) impedance with cell divider synthesis,(2) restraint of protein blend, (3) interference with nucleic corrosive union, (4) hindrance of a metabolic pathway [13]. The effectiveness of β-lactam antibiotic depend on their ability to form covalent linkage with target site [21]. Antibacterial medications that work by repressing microscopic organisms cell divider blend incorporate the b-lactams, for example, the penicillins, cephalosporins, carbapenems, and monobactams, and the glycopeptides, including vancomycin and teicoplanin [8].

PBPs are characterized as those bacterial proteins that predicament penicillins and other fJ-lactam anti-infection agents covalently. PBPs are promptly distinguished and their relative sums quantitated by brooding of bacterial films with [14C] penicillin G, trailed by sodium dodecylsulfate (SDS) gel electrophoresis and ftuorography [5]. The liking of a PBP for guaranteed (non-radio labeled) fJ-lactam is normally communicated as the grouping of anti-microbial required to lessen [14C]penicillin-G authoritative to the PBP by half and is resolved after preincubation with the unlabeled fJ-lactam under given states of time, temperature [5]. Studies went for reasoning which PBPs are deadly focuses for f3-lactam anti-microbial have used two key methodologies: examination of mutants with adjusted PBP examples and relationships between's in vivo and in vitro impacts of fJ-lactams. In this manner, the physiological results of inactivation of specific PBPs, either by change or by treatment with exceptionally particular fJ-lactams, have been inspected and the in vivo elements of the PBPs inferred [5]. β-Lactam specialists restrain synthesis of the bacterial cell divider by meddling with the compounds required for the blend of the peptidoglycan layer. Vancomycin and teicoplanin additionally meddle with cell divider amalgamation, yet do as such by official to the terminal D-alanine buildups of the incipient peptidoglycan chain, along these lines keeping the cross-connecting steps required for stable cell divider synthesis [13]. Notwithstanding penicillins and cephalosporins, the vancomycin group of glycopeptide anti-microbials additionally focuses on the cell forming peptidoglycans. But instead than focusing on the catalysts engaged with peptide crosslinking, vancomycin ties up the peptide substrate and in this manner keeps it from responding with one of the transpeptidases or transglycosylases. The net impact is the same: inability to make crosslinking of peptidoglycans prompts a weaker divider that inclines the treated microbes to a lysis of the cell wall layer. The container molded base of the vancomycin anti-infection makes five hydrogen bonds to the D-Ala-D-Ala dipeptide end of each uncrosslinked peptidoglycan pentapeptide side chain, which represents the high fondness of the anti-microbial for its objective, both in halfway crosslinked dividers and in the lipid II middle of the road. Since β-lactams and vancomycin chip away at contiguous advances - substrate and catalyst , they indicate cooperative energy when utilized as a part of combination [4]. For anti-microbials to be compelling they should achieve their particular bacterial targets and collect at fixations that can demonstration in some sensible time period. For instance, the protein-amalgamation hardware is situated in the cytoplasm so antibacterials that are inhibitors of protein union must go through the cell films (external andinner porousness obstructions for Gram-negative microscopic organisms; internal layer hindrances for Gram-positive microbes) and after that collect to a sufficiently high focus to hinder the specific vulnerability advance of protein get together. Both Gram-positive and Gram-negative microscopic organisms that wind up plainly impervious to antibiotic medications generally overproduce related film proteins (with relative sub-atomic masses of 42,000) that go about as a fare or efflux pump for the drug [4].

A structural representation of penicillin binding protein from *Staphylococcus aureus* is shown below. It shows penicillin like antibiotic binding site, non active sites and transpeptidase region (domain which is responsible for the synthesis of cell wall in bacteria).

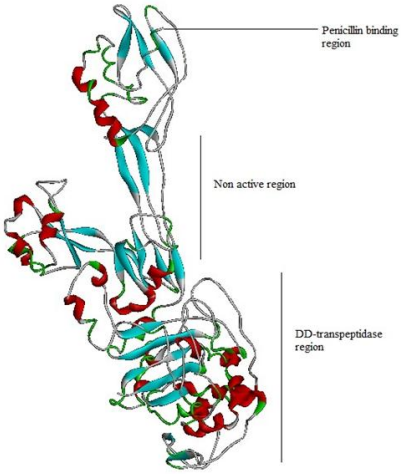

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Fig: 1 Structure of penicillin binding protein 2A from Methicillin-Resistant *Staphylococcus aureus* strain 27R showing the β-lactam binding site, non active region and transpeptidase area.

DRUGS AND COMBINATIONS

Tetarimycin A, Tetarimycin A (1) is an anti-infection with movement against methicillin-resistant *Staphylococcus aureus* (MRSA) identified through Induced Expression of Environmental DNA Gene Clusters [22]. It is gram positive particular anti-microbial with strong action, The structures of 1 and a noteworthy dormant metabolite, tetarimycin B, were illustrated utilizing a mix of high-determination mass spectrometry (HRMS) and NMR information . The structure (1) was additionally accordingly affirmed by single-precious stone X-beam diffraction analysis (information from which were kept with the Cambridge Crystallographic Data Center under promotion number CCDC. The two mixes are novel tetracyclicnatural products [22].

Synergism of vancomycin with other antibiotics

Vancomycin is regularly joined with a moment anti-microbial, frequently rifampin or gentamicin, for the mitigation of genuine methicillin-resistant *staphylococcus aureus* infections [23]. Theoretical explanations behind the utilization of anti-infection agents in mix with vancomycin for the treatment of genuine methicillin-resistant S. *aureus* (MRSA) contamination incorporate the accompanying:

To widen scope to incorporate VISA and heteroresistant VISA and to enhance action against secludes with a base inhibitory

focus (MIC) at or drawing nearer the breakpoint for powerlessness
To keep the development of decreased vulnerability to vancomycin
To give movement against stationary-stage life forms and creatures developing in biofilm
To enter cells and tissues not came to by vancomycin [23].
Vancomycin in addition with rifampin and gentamicin, relevant procedures for the treatment of prosthetic valve endocarditis (PVE) caused by MRSA suggest the utilization of the 3-medicate mix of vancomycin, rifampin, and gentamicin, with the aminoglycoside controlled for just the initial 2 weeks of treatment . Interestingly, the rules don't prescribe the expansion of rifampin to vancomycin for the treatment of native valve endocarditis because of MRSA. The proposal for the 3-medicate blend in the treatment for MRSA. PVE has all the earmarks of being an extrapolation from the suggestion for the treatment of PVE because of S. epidermidis , which, evidently, is prevalently in view of a review investigation of an aggregate of 26 patients getting different regimens, with or without attendant surgical treatment . In that review, 19 of the 26 patients got consolidated medicinal and surgical treatment, leaving 7 for whom anti-toxin treatment was assessable just 1 of whom got vancomycin monotherapy [23]. Nisin, an antibacterial substance delivered by Lactococcuslactis (once in the past *Streptococcus lactis*, Lancefield bunch N), found over 80 years back, is generally utilized as a sustenance additive. It is viewed as a bacteriocin, however is atypical in having a wide range of movement against Gram-positive bacteria.1 Nisin is a polypeptide containing 34 amino corrosive deposits (mol. wt 3353), including the strange mixes lanthionine and β-methyllanthionine: therefore it isclassed as a 'lantibiotic is additionally used to treat MRSA [24].
The in vitro action of the oxazolidinone linezolid was contemplated alone and in mix with three anti-microbials following up on various cell targets. Oxazolidinones are bacterial protein amalgamation inhibitors that demonstration at a beginning time by keeping the arrangement of the start complex. Mixes of linezolid with gentamicin, vancomycin or rifampicin were assessed against for methicillin-resistant *Staphylococcus aureus* strains, utilizing murdering bends in conjunction with examining electron microscopy. Linezolid in addition to rifampicin had all the earmarks of being the most dynamic mix against methicillin-resistant S. *aureus* strains in time– kill experiments [25].

NEW TREATMENT APPROACHES AND THERAPEUTIC ALTERNATIVES

In the recent time it has been said that MRSA infections in the western countries like America has increased and mortality rate is increased than the AIDS. Life threatening diseases are caused by toxins from CA-MRSA strain like Panton- Valentine Leukocidin (PVL) and Phenol-Soluble Modulins (PSM) [26]. About three half of the infection affects skin and soft tissues in the body. There are several drugs which were introduced into the action and were got resisted. A phage therapy was also experimented. There are some conditions to be fulfilled for getting an effective antibiotic like antibiotic target must exist inside the bacterial cell, effective amount of antibiotic must be reached in targeted site, the antibiotic should not get metabolized. Introduction of third generation cephalosporins shows a wide coverage using a single therapeutic agent. Number of studies has shown that monotherapy is better than combination therapy Daptomycin, a cyclic lipopeptide antibiotic was used to treat both CA-MRSA and HA-MRSA. It acts by disrupting the bacterial cell wall leading to its lysis. It was accepted due to its safe line but it got inactivated by pulmonary surfactants. Vancomycin was used to overcome the infection. It was selected due to its safe profile and insufficient active drug. Use of this was stopped due to the evolution of Vancomycin Intermediate Resistant *Staphylococcus aureus* (VISA). Methanolic extract of *Samadera indica* have good bactericidal activity against S. *aureus* [27]. Chemotherapy using linezolid was limited due to its expenses. There several antibiotics like glycylcycline antibiotic, cephalosporins (due to its affinity on PBPs) were used [28]. There are several researches undergoing to develop new drugs with a novel action against MRSA. Development of novel drugs should be able to overcome the resistance offered and its actions should involve shortening the therapy schedule, harmful effects should be reduced or eradicated, moreover the resistance should be eradicated and the combination therapies must have excellent efficacy. A research has been done to find the anti-inflammatory activity of *Mirabilis jalapa* Linn. and found that alcoholic and petroleum ether extract show good anti-inflammatory action [28]. Contemporary details of the research can be sited in several web sites. Some of the recent studies in MRSA had came out and several industries are working to get a result. Some of the studies and inventions of different companies are mentioned below :
Table contains array of drugs and their method of inhibition. Some of them are under clinical studies.

Table: 1 showing antibacterial agents with their mode of action and some compounds under clinical trials by several industries [28].

Drug	Mode of action
Oritavancin	Inhibition of peptidoglycan biosynthesis
Dalbavancin	Inhibition of peptidoglycan biosynthesis (lipoglycopeptide)
TD-1792	Inhibition of peptidoglycan biosynthesis
Mupirocin	Inhibition of bacterial protein synthesis by inhibiting isoleucyl tRNA synthase
Iclaprin	Inhibition of dihydrofolate reductase
XF-73	Depolarization of cytoplasmic membrane
TP-434	Inhibition of bacterial protein synthesis by targeting ribosome
BC-3781	Inhibition of protein synthesis by targeting 50S ribosomal subunit
BC-7013	Inhibition of protein synthesis by targeting 50S ribosomal subunit
BC-3205	Inhibition of protein synthesis by targeting 50S ribosomal subunit
RX-1741	Inhibition of protein synthesis by targeting 50S ribosomal subunit
Tedizolid	Inhibition of protein synthesis by targeting 50S ribosomal subunit
Tomopenem	Inhibition of bacterial cell wall synthesis by binding to penicillin binding protein
Cethromycin	Inhibition of protein synthesis by targeting 50S ribosomal subunit
NX-103	Inhibition of protein synthesis by targeting ribosomal subunit (synergistic effect)
Delafloxacin	Inhibition of bacterial gyrase
LBM-415	Inhibition of bacterial protein synthesis by inhibiting peptide deformylase
GSK1322322	Inhibition of bacterial protein synthesis by inhibiting peptide deformylase
MSI-78	Formation of an amphipathic α-helical peptide on membranes that induces pore or changes membrane permeability
OligoG CF-5/20	Immunomodulating activity
F598	Inhibition of virulence by targeting the PNAG carbohydrate of the bacterial capsule.

CONCLUSION

The era of antibiotic dominance has been coming to extinct after the brunt of bacteria against antibacterials. Growing infections are impossible to treat and leads to severe health care risks. WHO mentioned that newly discovered agents are not effective against highly resistant bacteria. Most of the phyto constituents are having effective antibacterial effect but the technique of isolation and search should be systematically done to get a proper effective antibiotic with safer margin of action. Since the present antibiotics are resisted in action, novelty of new antimicrobial must overcome it.

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