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Evolutionary approaches to combat antibiotic resistance in Microbes

Sunita Rani[1], Priyanka[1], Sonam Sharma[1], Tinku[2], Rajesh Kumar[3], Vinay Kumar[3]

[1]Research Scholar, Department of Microbiology, RIMT University, Mandi Gobindgarh, Punjab, India

[2]Masters in Medical Laboratory Sciences, Charles Darwin University, Darwin, Australia

[3]Assistant Professor, Department of Paramedical Sciences, Guru Kashi University, Talwandi Sabo, Punjab, India

[4]Assistant Professor, Department of Medical Laboratory Science, RIMT University, Mandi Gobindgarh, Punjab, India

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ABSTRACT

Antibiotics are one of the most important discoveries yet on earth. However, the rise of antibiotic resistance among microorganisms has lowered their potency of treatment for diseases which is now becoming life-threatening to patients. In this context, the present review discusses the reason for the development of resistance among bacteria through their mechanisms and evolutionary approaches to address this issue. Quorum sensing inhibition, bacteriocins, nano therapy, phage therapy, and essential oils have been discussed in the present work.

Keywords: Antibiotics resistance, Nano therapy, Quorum sensing, Bacteriocins

INTRODUCTION

Microorganisms produce secondary metabolites called antibiotics. These antimicrobial substances with low molecular weight aid in destroying or preventing the growth of microorganisms. The word "antibiotic" was first used by ``Waksman`, who expanded its definition to include any substance that aids in the destruction or inhibition of the growth of another microorganism. Based on the type of effect they will have on a certain microorganism, antibiotics are categorized into two categories:

- **Cidal impact:** Antibiotics with this property kill other bacteria by exerting a cidal effect.
- **Static effect:** A static effect is one that merely prevents growth.

There are antibiotics that have a narrow or broad spectrum. To illustrate how various antibiotics affect various types of microorganisms, the spectrum of actions reflects the range of those medications.

- **Broad Spectrum Antibiotics:** Antibiotics work against both for gram-positive and gramnegative bacteria and variety of other microorganisms are referred to as broad-spectrum antibiotics.
- **Narrow Spectrum Antibiotics**: Narrow spectrum antibiotics is that which exclusively works against gram-positive as well as negative bacteria.

- **Limited Spectrum Antibiotics:** In this category, Antibiotics only work against a single type of microorganism.

Table-1 Microbial source of some antibiotics and mechanism of their action and the target

ANTIBIOTICS	MICRO-ORGANISM	TARGET	MECHANISM OF ACTION
Penicillin	*Penicillin sp.*	Cell wall cross-linking	Cell wall synthesis inhibition
Bacitracin	*Bacillus sp.*	Cell wall cross-linking	Cell wall synthesis Inhibition
Kanamycin	*Streptomyces sp.*	16s rRNA	Protein synthesis inhibition
Neomycin	*Streptomyces sp.*	16s rRNA	Protein synthesis inhibition
Streptomycin	*Streptomyces sp.*	30s rRNA	Protein synthesis inhibition
Chloramphenicol	*Streptomyces sp.*	Peptide;transferase	Protein synthesis inhibition
Erythromycin	*Streptomyces sp.*	23s rRNA	Protein synthesis inhibition
Actinomycin D	*Streptomyces antibioticus*	Bind DNA	Block RNA synthesis.

Bacteriocin: Many *Staphylococcus epidermidis* strains produce antibacterial peptides (lantibiotics) that contain lanthionine, one of the kinds of bacteriocin. Lactibiotics and class ii bacteriocins are the two categories of bacteriocins that gram-positive bacteria produce (1). In place of conventional antibiotics, bacteriocin works (2). To destroy the bacteria, these proteins can unite with the appropriate receptor on another microbe. It functions as an antibacterial medicine, a revolutionary anti-cancer drug, and it has the potential to replace antibiotics. It functions as a significant inhibitor of several animal and plant infections, including *enterotoxigenic E. coli, VRE, methicillin-resistant Staphylococcus aureus,* etc.

A bactericidal mechanism of bacteriocin is mostly demonstrated through receptor binding on bacterial surfaces. It exhibits anti-tumor action and is used in cancer therapy (3).

The manufacturing of antibiotics is the foundation of this thesis. Staphylococcus-produced antibiotics and how they combat various bacterium cells. *Staphylococcus epidermidis* will first be identified using the pure plate and spread plate techniques. After that, *Staphylococcus epidermidis* culture is subjected to an additional 11 biochemical tests and four sugar fermentation assays in order to identify the required bacterial strain. Additionally, an antibiotic will be isolated and tested for sensitivity to *Pseudomonas aeruginosa* using the AST (Antibiotic Susceptibility Test) method.

Review of Literature:

Microbes or microorganisms are tiny. Microorganisms are defined as organisms with one cell, several cells, or clusters of cells. Microorganisms, which are minuscule, are both vital to living and can occasionally be harmful. A phylogenetic tree based on rRNA sequence data classifies microorganisms into six different categories, which are then divided into three separate domains. These six types include bacteria, archaea, protozoa, fungi, algae, and viruses. Bacteria are separated into Gram +ve and Gram-ve bacteria using the "Hans Christian Gram`` method of straining.

GRAM NEGATIVE BACTERIA

Gram-negative microorganisms are classified by the color they turn after a chemical process called a Gram

stain. When using this technique, gram-negative microorganisms appear red. Gram negative microorganisms are in a protective capsule. This pill helps prevent bacteria from eating up the white blood cells that fight infections. Gram-ve microorganisms have an outer membrane that protects them against several antibiotics. When this membrane is damaged, it leaks endotoxins, which are deadly substances. Endotoxins affect the severity of signs and symptoms of infections caused by gram-negative microorganisms.

GRAM POSITIVE BACTERIA:

Gram-positive bacteria are identified by a specific staining technique in which crystal violet dye is held in place by the thick peptidoglycan cell wall. Microorganisms that are gram-negative are contained in a protective capsule. This supplement aids in the prevention white blood cells, which fight *Staphylococcus*, grows in the form of clusters and are catalase-positive, and *Streptococcus*, grows in chains system and are catalase-negative, are examples of gram-positive cocci. Again, the genus Staphylococcus is divided into coagulase-positive and coagulase-negative strains, such as Staphylococcus aureus and Staphylococcus epidermidis. In addition, gram-negative bacteria have a weaker peptidoglycan layer and an outer covering membrane that prevents them from attaching to the blue dye used in the initial staining step. Staphylococcus: The cocci-like bacteria of the genus Staphylococcus are best known because they are abundant on the mucous membranes and skin of mammals and other warm-blooded animals. A cell that tends to clump together into grapelike clusters is called a staphylococcus. These bacteria are classified as Gram-positive because they do not form spores, lack motility, and are facultative anaerobes.

Staphylococcus aureus and *Staphylococcus epidermidis* strains are extremely important to humans. Furthermore, *Staphylococcus epidermidis* is a minor infection that affects only persons with limited resistance. In addition, Staphylococcus aureus is the most common food spoilage bacterium and is a major cause of blood poisoning, abscesses and other skin diseases in humans. It also causes meningitis, pneumonia, urinary tract infections, and mammary gland or udder disease in humans and domestic animals. Toxic shock syndrome has also been caused by local staphylococcal infections. It is a disease caused by a toxin entering the bloodstream from an infection site, usually caused by an antimicrobial peptide from a bacterium.

Staphylococcus aureus (MRSA) is currently one of mankind's top worries for methicillin-resistant and also known as MRSA. It may be distinguished by a single change makes it methicillin resistant. On the other hand, a semi-synthetic derivative of penicillin is an antibiotic used to treat antibiotic resistance in staphylococcal infections. Methicillin resistance emerged when methicillin was first used against Staphylococcus aureus in the early 1960s. Methicillin seems to be no more used, yet the variant of MRSA that it created is still often found on skin surface, nostrils, bloodstream, or urine. According to recent studies, about 50 million individuals worldwide are likely to carry MRSA, which is spread through skin exposure but rarely causes illness in healthy individuals. Furthermore, it is suspected that very young children, the elderly, and which are in hospitals and nursing homes are to be especially prone to MRSA infection, is challenging to treat due to widespread antibiotic resistance. Vancomycin, on the other hand, is regarded a final line of defence in the therapy of MRSA infections. Excessive usage of vancomycin, by contrast side, leads to growth of *vancomycin-resistant Staphylococcus aureus (VRSA)*, despite which only a few medications are helpful. In the United States in 2005, around 18,000 deaths were found that were completely driven to *methicillin-resistant Staphylococcus aureus* (MRSA), which surpassed the number of people who died by HIV/AIDS, which was close to 17,000. These findings highlights the crucial need for increased supervision to prevent and regulate the expansion of these highly dangerous bacteria (4).

Staphylococcus epidermidis: Staphylococcus epidermidis infections are common in patients with weakened immune systems or those confined to hospitals. These are found on the skin surface and mucous membranes without causing any harm, but if they penetrate our bodies, they cause chronic disease.

The coagulase activity of *Staphylococcus epidermidis* distinguishes it from *Staphylococcus aureus. Staphylococcus epidermidis* lacks coagulase, but *Staphylococcus aureus* does.

When grown in anaerobic settings, *Staphylococci* create lactic acid, which is one of their most essential metabolic characteristics. *Staphylococcus epidermidis* physiological purpose is unknown, however it is thought to aid in skin lipid metabolism and act as a main barrier against invading pathogens.

All hospital illnesses are caused by *Staphylococcus epidermidis*. Under a light microscope, it appears spherical with an average diameter of 0.5-1.5um and forms irregular clusters. Furthermore, it develops unique colonies on various agar medium, such as round, cream-colored colonies on nutritional agar, tiny pink to red colonies on mannitol salt agar, and white colonies on tryptic soy agar (5).

Staphylococcus epidermidis shows antibiotic resistance due to the presence of antibiotic resistance genes, which makes treatment difficult. In addition, biofilms and multicellular aggregates have inherent resistance and tolerance to antibiotics. Furthermore, recent bacterial research resulted in the detection of certain molecular markers that allow *Staphylococcus epidermidis* immune infiltration but also, additionally, its ability to induce chronic disease in humans when infected. Furthermore, these causes are about to serve original functions in the microorganism's non-infectious existence and reveal the unintentional nature of allowing *Staphylococcus epidermidis* infections which assists in discriminating between translocation, contamination, and infection. To assess treatment strategies against *S.epidermidis* infections a deeper understanding of *S.epidermidis* physiological behavior is necessary.

Certain strains of *Staphylococcus epidermidis* can also modify the host's innate immune response, especially TLR 2, allowing the host to fight infections. *Staphylococcus epidermidis*-produces n-phenyl components have been demonstrated to specifically supressed pores and skin pathogens, like as *Staphylococcus aureus* as well as Group A *Streptococcus*, or to facilitate their clearance when paired alongside host antimicrobial peptides (AMPs). *Staphylococcus epidermidis* also stimulates keratinocyte AMP expression by a TLR2-structured mechanism. This shows that all pores and skin commensals have a close relationship with the host's innate immunity. Microdissection of epidermal cells of the epidermal and adipose tissue identified by 16S ribosomal RNA sequencing, revealed that *Staphylococcus epidermidis* proliferation influences T-molecular homing and characteristic in an IL-1 structured way.

According to other recent research, *Staphylococcus epidermidis* may also preserve against dermal neoplasia by producing 6-N-hydroxyaminopurine, a chemical that prevents DNA polymerase activity. Furthermore, butyric acid, which is generated through *Staphylococcus epidermidis*, allows adipose-derived tissue to develop into adipocytes and lipid accumulation inside the cytoplasm, which leads to better layer of the skin (6).

Staphylococcus epidermidis pathogenicity is now recognised due to the biofilm membrane that forms on the surface of infected tissues, which aids in the increase of bacterial resistance to specific antibiotics. To summarise, understanding the suppression of biofilm formation and screening biofilm inhibitors will give a significant benefit in lowering bacterial drug resistance, which will also improve knowledge of preventing and treating biofilm-associated infections (7).

Furthermore, *Staphylococcus epidermidis* was formely assumed to be a beneficial commensal bacteria on skin surface but is now known to be the most prevalent cause of nosocomial infection. Furthermore, when *Staphylococcus epidermidis* penetrates the human body, it might cause chronic illness. It can withstand high salt concentrations because to eight sodium ion exchangers on the cell membrane and six osmoprotective transport systems [8].

Staphylococcus epidermidis infections, on the other hand, are classified as one of the prototypic biofilm-associated infections and are also considered dynamic. Surface contact between planktonic bacterial cells is also important for biofilm development. As all cells succeed in attaching to a surface, this results in cell attachment, surface motility, and finally binary division, which aids in the aggregation of bacterial attachment. Furthermore, all of these basic cell aggregates produce exo-polymers such exo-polysaccharides and extracellular proteins, which aid in the creation of the extracellular matrix. Furthermore, many components, such as extracellular DNA, are derived from lysed cells (eDNA). As a result, multicellular, multilevel biofilm architecture is being developed. Separation of biofilm cells and clusters aids in the spread of biofilm-associated infection in the latter stages of the biofilm formation cycle and is a critical step throughout the cycle (7).

ANTIBIOTIC AND ANTI-MICROBIAL PEPTIDES :-

Antibiotics are secondary metabolites that microorganisms create. These are antimicrobial compounds with low molecular weight that help kill or prevent the development of microorganisms. Waksman created the word antibiotic; a wide definition of an antibiotic is a substance that aids in the death or inhibition of the development of another microorganism [9].Many *Staphylococcus epidermidis* strains generate lanthionine-containing antimicrobial peptides (lantibiotics), which are a form of bacteriocin. Gram-positive bacteria create two types of bacteriocins: lactibiotics and type ii bacteriocins (1).

Bacteriocin is produced differently by Gram-negative and Gram-positive bacteria. Colicins are 2580 kDa gram-negative bacteriocins expressed by the bacteria's genome and plasmid. Bacteriocins produced by Gram-positive bacteria, on the other hand, have features similar to microcins. Bacteriocins with a low mass compared with fewer than 60 amino acids are encoded. Furthermore, lactic acid bacteria (LAB) produce a diverse range of bacteriocins with differing sizes, configurations, physico-chemical properties, and inhibited spectrum.

The bacteriocins of gram-positive species are differentiated into 3 major classes :-

1. class I (modified proteins, lantibiotics)
2. class II (unmodified peptides, non-lanthionine)
3. class III (non-lanthionine) (large proteins, heat unstable).

S. epidermidis produces antimicrobial peptides, including lanthionine (lantibiotics). Class I peptides are post-translationally modified small membrane energy bacteriocins or lantibiotics. Lactacin F and ABP- are essential for class IIb bacteriocins to form fully energetic pore complexes. Cyclic peptides of bacteriocins, like epidermycin NI01 and lactococcin A class IIe bacteriocins, are straight non-pediocin-like 1s with post-translational alterations of the siderophore-type serine-rich carboxy-terminal region containing microcin E 92. one bacteriocin. Class IIe bacteriocins should be classified as Gram-negative microcins because Microcin E 92 is derived from *Klebsiella pneumoniae*, which is not necessarily a Gram-positive bacterium (10).

Bacteriocin against *Staphylococcus aureus*:-

Staphylococcus aureus leads to disease atopic dermatitis (AD). *Staphylococcus epidermidis*, on the other hand, generates class I thermostable bacteriocins that aid in the death of *Staphylococcus aureus*. There is a critical need for the development of specific medicines that exclusively target *Staphylococcus aureus* and do not affect other beneficial microbiomes.

Atopic dermatitis is a characterized by inflammation on skin that produces dry skin, eczema, and severe itching. Despite its intricacy, the etiology of Atopic Dermatitis is connected to the epidermal microbiome (11).

Moreover, Atopic Dermatitis is a inflammatory skin disease caused by skin barrier failure, which influences the bacterial ecology of the skin. Furthermore, the cell wall component lipids and teichoic acid of Staphylococcus aureus induces further epidermal barrier breakdown by inhibiting the formation of skin barrier molecules such as loricrin and filaggrin. Dysbiosis contributes to the cause of Atopic Dermatitis by both unfavourable bacterial effects and the loss of beneficial effects from certain skin microbiome members. Furthermore, Staphylococcus aureus emits pore-forming, phenol soluble components, or PSMs, -toxin, which contributes to further skin barrier deterioration and causes skin infections.

FIGURE 1 Atopic dermatitis (31)

Moreover, Atopic Dermatitis is a inflammatory skin disease caused by skin barrier failure, which influences the bacterial ecology of the skin. Furthermore, the cell wall component lipids and teichoic acid of *Staphylococcus aureus* induces further epidermal barrier breakdown by inhibiting the formation of skin barrier molecules such as loricrin and filaggrin. Dysbiosis contributes to the cause of Atopic Dermatitis by both unfavourable bacterial effects and the loss of beneficial effects from certain skin microbiome members. Furthermore, *Staphylococcus aureus* emits pore-forming, phenol dissolved components, or PSMs toxin, which contributes to further skin barrier deterioration and produces inflammatory reactions as fuel for dermal mast cells. As a result, people with Atopic Dermatitis always have a greater level of IgE antibiotics. The severity of Atopic Dermatitis is related to the generation of IgE particular for *staphylococcal* superantigens.

Many diverse investigations are now being conducted to improve our understanding of the skin microbiome's medicinal potential. *Staphylococcus epidermidis* is a powerful competitor that is employed in a number of techniques to combat *Staphylococcus aureus* infection. Bacteriocins are infrequently created by the human microbiota, and this antimicrobial peptide is active only against bacteria that are closely related. *Staphylococcus epidermidis* produces bacteriocins that are bactericidal to *Staphylococcus aureus*. This antimicrobial peptide-bacteriocins aid in the production of biochemical test showing coagulase-negative result *Staphylococcus* strains that are fewer common in atopic individuals than virulent strains, and the revival of these *Staphylococcus* strains aids in decreasing the activity of colonisation of Staphylococcus aureus. It has been shown that transplanting *Staphylococcus hominis* and *Staphylococcus epidermidis* strains cells producing antimicrobial peptides (AMPs) is extremely successful in regulating and preventing *Staphylococcus aureus* overgrowth. In contrast to this specific bacterium employed against *Staphylococcus aureus* as well as *Staphylococcus epidermidis* constitutes one of the most frequent infections that is a rising risk issue in hospitals globally and is recognised for hospital infection. Furthermore, because of the creation of a protective biofilm matrix on the human skin surface, it is frequently difficult to kill or suppress its virulent strains. As *Staphylococcus aureus* is an antibiotic-resistant species, bacteriocin that can target it has become a viable method for reducing *Staphylococcus aureus* colonisation and skin infection.

Staphylococcus epidermidis ATCC12228 is an important strain of *Staphylococcus epidermidis*. It is a non-virulent, non-infection associated, and non-biofilm producing strain that produces heatfixed class I lantibiotics and bacteriocins of minimal molecular weight. Furthermore, lowmolecular-weight proteins were generally absent from *Staphylococcus epidermidis ATCC12228* cell-free supernatant, and the bulk of the discovered proteins about 80% were anticipated to be cytoplasmic in this varity of *Staphylococcus epidermidis*. This demonstrates *Staphylococcus epidermidis ATCC12228* expresses but does not export these proteins (11).

***Staphylococcus haemolyticus* with Bacteriocin**:

Although *Staphylococcus epidermidis* was formerly regarded to be a helpful commensal bacteria on mucosal membrane, it is currently the most prevalent cause of nosocomial infection(8).

Bacteriocins are ribosomally synthesized antimicrobial peptides that show promise as new therapeutic options against multidrug-resistant pathogens such as *Staphylococcus aureus* and *Staphylococcus haemolyticus*. Hybrid 1 (H1) was designed to be active against staphylococci by joining the N- and C-side portions of similar bacteriocins Enterocin K1 (K1) and enterocin EJ97 (EJ97). I was. H1 functions as a substrate for the membrane-bound enzyme RseP and has potent antibacterial activity against *Staphylococcus hemolyticus*, one of the most common nosocomial infections. Because *Staphylococcus haemolyticus* is particularly isolated compared to the parent bacteriocin, H1 works effectively with broad-spectrum bacteriocins such as galbicin and micrococcus, killing plankton and biofilm-associated bacteria as well as *Staphylococcus haemolyticus.*

Recombinant Antibiotic:

Genetic recombination was initially little used compared to the widespread application of mutations in industry. Due to the low the genetic recombination of corporate microbes, this loss of hobbies became common even with early success requirements. Recombination was mistakenly thought of as an opportunity for mutation rather than a strategy to complement mutagenesis efforts. The best balanced and environmentally friendly pressure boosting strategy can now include both mutagenic screening and recombinant screening components. In this type of program, traces of a gene mutation line of varying degrees or strains produced by different ancestors can be recombined.

Such traces can vary in many genes, and their mixing results in genotypes that are not strictly mutational offspring of both parents. Recombination has become increasingly important in industrial gene sequencing. The similarity of genetics of *Streptomyces coelicolor* with other species of *Streptomyces*, such as *Streptomyces olivaceous,* and *Streptomyces Rimosus* was studied using genetic map.

New antibiotics are badly needed, despite gains in the antibiotic sector. The difficulties and significant expense of establishing unique antibiotic systems and shops with new modes of circulation for such purposes became obvious some 30 years ago, and the firm entered a slump period. However, efforts to find and design new antibiotics must be sustained in order to defend the world's population's health. This is owing to a mix of complementary technologies, including high-throughput screening for herbal products and innovative genetic technology. By combining producers of distinct or maybe comparable drugs, genetic recombination enables for the discovery of novel antibiotics. The method of protoplast fusion was utilized between *Streptomyces griseus* and *Streptomyces tenjimariensis* to produce a hybrid. Indolizomycin was generated by protoplast fusion between *Streptomyces griseus* and *Streptomyces tenjimariensis*. However, efforts to find and develop new medications must be sustained in order to defend the world's population's health. This is owing to a mix of complementary technologies, including high-throughput screening for herbal products and innovative genetic technology. Interspecific protoplast

fusion between Streptomyces griseus and five distinct species (*Streptomyces cyaneus, Streptomyces exfoliatus, Streptomyces griseoruber, Streptomyces purpureus, and Streptomyces rochei*) ultimately results in recombinants, 60% of which produced no antibiotics and 24% of which produced antibiotics unique, according to the figure traces. This strategy of combinatorial biosynthesis of antibiotics is becoming increasingly common in antibiotic manufacturing and discovery. New antibiotic substances were discovered because of the explication of biosynthesis processes and the identification of biosynthetic genes.

Techniques used are

- Focused gene disruption wherein genes are inactivated.
- Involving genes from other pathways
- Combination of Above

Over 200 new polyketides were synthesized via combinatorial biosynthesis.

3-0-Acetyl-4''-0-isovaleryltylosin (AIV) is beneficial in veterinary therapy over *tylosin-resistant Staphylococcus aureus*. It is made by first manufacturing tylosin using *Streptomyces fradiae*, then bioconverting tylosin with *Streptomyces* thermotolerance. A novel organism was produced by mixing plasmids containing acyl transferase DNA from *Streptomyces fradiae* and *Streptomyces thermotolerans*. Bacteriocin is efficient against *Staphylococcus* aureus, a bacterium that causes skin infections in humans and warm-blooded animals. The main purpose is to extract the bacteriocin.

Antibiotic resistant bacteria: -

Antibiotic-resistant microorganisms in our environment and surrounds include

- Methicillin-resistant *Staphylococcus aureus (MRSA),*
- Vancomycin-resistant *Enterococcus (VRE),*
- Multi-drug-resistant *Mycobacterium tuberculosis (MDR-TB)*
- Carbapenem-resistant *Enterobacteriaceae (CRE) (CRE)* bacteria in the intestine

Methicillin-resistant: Methicillin resistance in Staphylococcus aureus (MRSA) indicates that the MIC (Minimal Inhibitory Concentration) of Oxacillin is more than or equal to 4 microorganisms/ml. (12). This resistance arises because of mutations or variations in the chromosomally encoded protein that is required for Penicillin-binding (13).

The presence of a particular gene sequence 'mecA', which is employed in the synthesis of transpeptidase PB2a and alters the organism's affinity of interacting with antibiotics, is the primary cause of Methicillin-resistant Staphylococcus aureus resistant to antibiotics such as Beta-lactams (14).

MRSA infections are classified into two kinds based on their mode of action, spread, and safety measures: hospital-related MRSA infections and community-related MRSA infections [12]. This disease is most typically observed in organisms. This infection, termed as HA-MRSA, is most typically encountered in organisms connected with health care institutions like as hospitals or clinics.

The presence of a particular gene sequence 'mecA' in Methicillin-resistant *Staphylococcus aureus* induces antibiotic resistance to Beta-lactams. HA-MRSA infections are linked to devices or anything invasive, such as surgeries, and HA-MRSA is a highly contagious sickness that may be transmitted from one person to another simply by touching (14). While CA-MRSA spreads in bigger and more broad areas, this kind of MRSA is considered to arise in younger, previously healthy persons (15). *Staphylococcus aureus* Antibiotic resistance causes a wide range of disorders, including organ-specific infections like pneumonia, osteomyelitis (an invading infection), pleural effusion, skin and cutaneous (most common), empyema, meningitis, and septicaemia (16).

The clinical signs of Methicillin-resistant *Staphylococcus aureus* (MRSA) that humans managed to learn about this infection are that the skin becomes swollen, there is an occurrence of painful red bumps that look like pimples or spider bites, which quickly

turn into boils or abscesses that are very painful and require surgery to remove drainage.

The location of each of these symptoms will become hypersensitive and warm when touched. there will be pus or other forms of discharge on the skin, and all of these will be followed by a temperature. Infected endocarditis is also one of the diseases or infections caused by Methicillin resistant *Staphylococcus aureus* (MRSA), which would be connected to intravenous drug abuse and causes more morbidity and mortality than any other bacteria (12).

'Staph,' a common word for a type of *S. aureus* bacterium that is normally visible in just about one-third of the total community's skin or nasal region (17). Methicillin-resistant *S.aureus* are not dangerous bacteria until they penetrate a human body through some kind of cut or wound on the skin, and if a human itself is healthy, it will produce such little damage or minor skin concerns.

MRSA is classified into two categories, each with their own group of risk factors for both variants of Methicillin-resistant *Staphylococcus aureus* (12). Hospitals are a key risk factor for the first Hospital-associated MRSA (HA-MRSA) infections, and individuals with aging body's immune system are more likely to be affected by MRSA (18).

Methicillin-resistant *Staphylococcus aureus* would invade our bodies through a route provided by various invasive medical devices such as healthcare tubing and intravenous lines (19). Community-associated MRSA (CA-MRSA) infections are mainly linked to skin-to-skin interaction, such as through wounds, scratches, or injuries, or in the presence of a crowd, especially in situations where hygienic conditions are not available (20). People who have the Human Immunodeficiency Virus (HIV) and those who use illicit injectable substances are more likely to get this illness (12).

When there are serious Methicillin-resistant *Staphylococcus aureus* (MRSA) illnesses such as communicable diseases in joint or bone and endocarditis, and there is small sensitivity of Methicillin-resistant *Staphylococcus aureus* (MRSA) to Vancomycin, i.e., Vancomycin-resistant *Staphylococcus aureus* (VISA or VRSA), people infected must seek advice from physician specialists in communicable diseases (12).

Vancomycin-resistant *Enterococcus* (VRE) :-

Enterococci are a kind of bacteria that is often encountered in the environment and in the body, including the stomach, genital tract, and skin [21]. It had no adverse effects on human bodies until it acquired resistance to antibiotics, notably to Vancomycin, which resulted in a variety of infections that were hazardous to the health of the elderly, those with weakened immune systems, and individuals who were already ill [22]. This infection has no single source of entry, but it generally begins to affect the body when it reaches the circulation, heart muscle, brains, urinary system, comes into touch with injuries on our skin, and other sterile areas.

It was formerly quite straightforward for scientists to mend ailments caused by *Enterococci* using Vancomycin, which effectively heals the disorders. However, Vancomycin resistance evolved in *Enterococci* over time, and they were called Vancomycin-resistant *Enterococci.* The primary *Enterococci* species responsible for diseases are vancomycin-resistant *Enterococcus faecium* and vancomycin-resistant *Enterococcus faecalis*, both of which are resistance to vancomycin [23] *Enterobacter faecalis.*

Vancomycin-resistant *enterococci* :- When patients ingest vancomycin or other medications on a routine basis when the bodies do not require them, they acquire enterococci (VRA), a disease caused mostly by this behavior. This antibiotic will remove any existing antigens in the body, but certain bacteria will not be destroyed by it, thus they begin to change their genetic composition. This makes them more difficult to kill and provides them with antibiotic resistance. Vancomycin resistant *enterococci* (VRE) may only transfer from one person to another by body

interaction, including touch contact with patients or employees at healthcare institutions, or by coming into contact with objects infected by the patient's touch [5,8]. If you are healthy and have a strong immune system, you have a low risk of developing VRE Vancomycin-resistant *Enterococci.* It cannot be transmitted by sneezing or coughing, like other virus infections which are also airborne transmitted [24].

The symptoms of *vancomycin-resistant enterococci* (VRE) vary depending on the location or organ infected [9].

For instance, if a person has an infection brought on by a wound, the area where the infection occurs becomes red or begins to burn. Back discomfort and a burning feeling when urinating are symptoms of an infection in the urinary system, which can also cause back pain. Additionally, some individuals have infections that are causing fever or chills, diarrhoea, weakness, and illness [24].

Vancomycin-resistant Enterococci **(VRA)** infections are associated with a number of risk factors, the most of which include hospitalisation, medication use, and aging [24]. These individuals are more likely to get this infection than those who are young and healthy. The immune system may be weakened by prolonged medication use and less able to respond to foreign particles entering the body [24]. People who have trouble emptying their urine and use catheters or IVs to help them do so are also susceptible to developing *vancomycin-resistant enterococci* (VRA) in their bodies [23].

Multi-drug-resistant Tuberculosis-causing *mycobacterium* (MDR-TB)

Multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) is a type of disease called tuberculosis that develops when bacteria exhibit high levels of resistance to the most strong and effective medicines, isoniazid, and rifampicin [25]. Different causes contribute to the resistance to these two medicines. Resistant to isoniazid medications develops as a result of changes and mutations at one of two key locations, the katG or inhA genes [9,10]. Rifampicin resistance is produced by a single nucleotide in the rpo gene, which codes for the beta subunit of DNAdependent RNA polymerase [3].

Tuberculosis is classified into two varieties: drug-resistance tuberculosis and drug-susceptible tuberculosis, and both types of tuberculosis are transmitted in the same way [25]. Tuberculosis is a contagious illness that is transferred through the air rather than through human contact. If an infected individual transmits the bacterium that causes TB in the air, whether by sneezing, coughing, or any other manner, another person who breathes in the germs will get sick. Physical contact, such as touching, sharing, and contacting, does not spread this disease.

MDR-TB causes a variety of symptoms that can be used to diagnose tuberculosis, including abrupt weakness, nocturnal sweats, fever, chest discomfort, illness and weight loss, coughing, and, in some cases, bleeding [26]. The symptom of tuberculosis varies depending on the location of the infection. Multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) is highly prevalent among persons who have Tuberculosis but are not following a suitable schedule for their treatments as prescribed by doctors and are taking such meds on alternate days rather than daily. It is possible that a person who has previously been infected with Tuberculosis will get infected with Multidrugresistant Mycobacterium tuberculosis (MDR-TB) because of the capacity established by Mycobacterium tuberculosis to resist drugs. Multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) is quite frequent among persons in some parts of the world. If a person arrives from that location or comes into touch with somebody who is suffering from it, they are more likely to become infected with Multidrug-resistance *Mycobacterium tuberculosis*.

Carbapenem-resistant *Enterobacteriaceae* (CRE) gut bacteria: -

Carbapenem-resistant *Enterobacteriaceae* (CRE) are bacterial strains that develop resistance to the medicines used to kill or cure Carbapenem-class infections. Superbugs are bacteria that cause diseases and develop antibiotic resistance (27). When *Carbapenem-resistant Enterobacteriaceae* (CRE) superbugs enter human bodies, they begin to interact with good bacteria and share their characteristics. *Carbapenem-resistant Enterobacteriaceae* (CRE) superbugs cause infections in several regions of the body, including the bladder, blood, and other organs [28]. This virus is also contagious and spreads by physical contact with infected persons, such as shaking hands or interacting with any health worker working in a contaminated area or managing with any such sufferer [27].

People who have been in hospitals for a long time, are suffering from disorders that require assistance to perform their daily life routines such as bathing, are surviving on breathing devices such as ventilators, or have any type of illness that is considered serious have a higher chance of becoming infected from such an infection than those who are not.

Ambler A class, B class, and D class carbapenemase antibiotics are grouped into three groups (29). The most prevalent of these three groupings is

- Class A, which contains two kinds of antibiotics, KPC and IMI. KPC is an abbreviation for *Klebsiella pneumoniae* carbpenemase, which is the most common gene in the Carbpenemase group across all cpCRE, and IMI is an abbreviation for Imipenemhydrolyzing beta-lactamase (4).
- Class B Carbapnemase antibiotics are also known as Metallo-Beta-Lactamases (MBL). IMP (Imipenem-resistance *Pseudomonas*), VIM (Verona integron coded Metallolactamase), and NDM (New Delhi Metallo-lactamase) are the three primary enzymes included in Class B[4].
- The last group of Carbapenemases Class D consists of OXA (Oxacillin-hydrolyzing Carbapenemase) which has genotypic similarities with gene ESBL making molecular testing difficult to identify between them (6,7,10). The OXA-48 is the most common form of OXA. Among all OXA kinds, OXA-48 is the most prevalent, and it is easily detected in *Klebsiella pneumoniae* (11).

Carbapenemases antibiotic resistant bacteria are typically found in plant vectors and other components that are transposable and allow them to move from one bacterium to another. Because of their considerable sequence variability (about 15-70%), these bacteria are difficult to distinguish during molecular testing (31).

Mechanism of Antibiotic resistance: -

Bacteria have certain inbuilt Resistance mechanisms to change, remove, and destroy antimicrobial agents (antibiotics) in order to combat them. *P. aeruginosa* outer membrane changes in response to aminoglycosides, In *S. pneumoniae*, efflux pumps remove quinolones from the cell. Target ribosomal active site modification using erm encoded methylases to limit attachment of macrolidsin *S. aureus, S. pneumoniae*, and *S. pyogenes*, Beta lactam enzymatic breakdown in Gram negative bacteria, Chloramphenicol antibiotic inactivation by chloramphenicol acetyl transferase in *S. pneumonia* (32).

1. Membrane permeability:

Gram negative bacteria are inhibited to antimicrobials than gram +ve bacteria because of the of an external outer lipopolysaccharide layer above the thin peptidoglycan membrane, which aids gramme negative bacteria in resisting the entry of hydrophobic antibiotics such as erythromycin or nafcillin (13). Bacteria use cellular membranes as their initial line of defence against antibiotics. When a cell is mutated, its susceptibility to antibiotics through the lipopolysaccharide layer changes.

Antibiotics such as beta lactams and glycopeptides exploit water-filled porins in the outer membrane to

target intracellular molecules or cytoplasmic membrane targets (33). To protect itself from hydrophilic antibiotics, the cell must suppress the production of porin channels. Clinical isolates have indicated that downregulating porin expression with mutant alleles of the polysaccharide layer results in carbapenem resistance in *Enterobacteriaceae*. In normal cells, this was previously controlled by carbapenemase-mediated enzymatic breakdown (34).

2. Efflux pumps:

Antibiotic efflux is one of the most frequently applied antibiotic resistance mechanisms and plays a critical role in antibiotic resistance. Efflux pumps (proteins) in the cellular membranes are designed to pump out a wide range of antimicrobial drugs and harmful compounds, preventing antibiotics including tetracyclines, macrolides, and FQ from entering the cell (fluroquinolones). The five families of efflux pumps include ABC (ATP binding cassettes), RND (resistance nodulation division), MFS (major formalized super), SMR (small multi - drug resistance), and MATE (multidrug and hazardous chemical extrusion) (35).

3. ABC family: -

ABC family transport systems are ATP-dependent transporters which are classified into two groups: homodimer and heterodimeric. The existence of degenerate ATP binding sites distinguishes heterodimeric transporters from homodimer transporters. NBDs (nucleotide binding domains) for ATP binding and hydrolysis and TMDs (transmembrane domains) for substrate binding are found in ABC transporters (36).

The best characterized efflux pump is found in *Streptomyces peucetiu*, where the efflux of two anticancer drugs, doxorubicin and daunorubicin, is mediated by the ABC family transporter proteins DrrAB, which are encoded by drrAB genes. DrrAB's efflux mechanism is based on ATP and GTP, and it is made up of two subunits, DrrA (Nucleotide Binding domain) and Drrb (transmembrane domain) (37).

4. RND family: -

RND (resistance nodulation division) proteins are larger in size than other membrane proteins. They are mostly homotrimer. However, certain RND transporter proteins have hetro and homo dimeric forms (secDF and HpnN)(39). RND transporters are further categorised into two groups: HAE-RND (hydrophobic and amphiphilic efflux RND) and HME-RND (heavy metallic efflux RND). In the case of Ecoli, there are five RND transporters belonging to the HAE-RND group (AcrAB, AcrAD, AcrEF, MdtAB, MdtEF) and one belonging to the HME-RND group (CusCFBA). These RND transporters aid in the elimination of secondary metabolites generated by Ecoli during its growth (40). The RND protein family is the active efflux pumps in *Pseudomonas aeruginosa*. It expresses four antibiotic resistance efflux pumps for the removal of -lactams as well as quinolones(41).

Campylobacter jejuni has the Cme triple multidrug efflux mechanism. The Cme locus is divided into three genes that code for three Cme active efflux polypeptide (CmeA, CmeB, and CmeC). Response to flouroquinolones and cephalosporins has recently emerged in Campylobacter, prompting the development of innovative treatment methods (41). *Neisseria gonorrhoea*, another sexually transmitted bacteria, has just one MtrCDE efflux mechanism. MtrD protein facilitates substrate transfer from the intermembrane space and trans - membrane space to MtrE peptide, which is found in the outer surface. MtrC protein works with MtrD and MtrE in the inner membrane (42).

5. The MFS family

MFS (Major facilitator superfamily) is a class of secondary active transporters that transport a wide range of substrates over biological membranes. They may be grouped further into than 70 families based on sequence homology. Based on their transport modes, MFS proteins are categorized into three types: uniport, symport, and antiport. Symport and antiport, for example, use energy stored in their co substrate to

transfer substrates over a gradient of concentration, whereas uniport simply carries material across a concentration gradient. MFS transport proteins are 400-600 amino acid length on average, having 12 to 14 probable transmembrane regions (TMS) (43).

Gram negative bacteria have a single operon that contains all of their genes. Encoding for a number of MDR MFS EPs made up of three-part complexes. It is primarily a regulatory gene, which is located near the genes involved MFS transporter proteins. It is expressed autonomously of the EP genes encoding (44) When it relates to the importance of MFS carriers in bacterial pathogenicity in host species, MFS EPs play a significant role in allowing bacteria to grow inside animal hosts. As an example. MdrM and MdrT coding genes in *L. monocytogenes* help the organism survive in bile-rich environments. Cholic acid, a component of bile, activates MdrM and MdrT EPs. This promotes the spread of *L. monocytogenes* inside this host organism. Just one of these 2 EPs, MdrT, helps *L. monocytogenes* survive in high bile conditions. Despite the fact that MdrM and MdrT collaborate in *L. monocytogenes* mouse liver colonization (45).

6. The SMR gene family

SMR are the tiniest proton motive pressure related multidrug resistant transporters (small multidrug resistance transporters). EmrE/MvrC/Ebr, AbeS, QacE, QacF, and other Smr transporter subclasses/members have been studied in a variety of microbiological species (47). The smr carriers cross the membranes with four -helical segments (TMS). The active H + /drug binding area of SMR proteins is located in the first TMS and is concentrated on a single evolutionary conserved Glu residue (48).

SMR proteins give resistance against a variety of hazardous lipophilic QCCs used as industrial surfactants, membrane disruption detergents, antiseptics, DNA-intercalating and toxic dyes, and reactive oxygen generating compounds (47).

7. MATE

The agent inducing multi - drug resistance in *Vibrio parahaemolyticus* was originally identified as multidrug and toxic compound extrusion, but it was later recognised in all domains of life. MATE is an electroneutral converter that uses the electrical impulse of H+ or Na+ as the driving force to export cationic compounds. As substrates, MATE acknowledges a wide spectrum of compounds with various chemical configurations. MATE is thought to be the cause of resistant strains in *Staphylococcus aureus*, which is a major problem in hospital infections and has garnered a lot of attention.

ALTERNATIVE METHODS USED IN ANTIBIOTIC RESISTANCE :-

1. **QUORUM SENSING INHIBITION:** In bacteria, quorum sensing (QS) is the mechanism responsible for a variety of activities including as plasmid transfer (conjugation), virulence, antibiotic resistance, and even bioluminescence. Quorum sensing is reliant on cell density and only becomes active when cell density is extremely high. As a result, this pathway contributes to transmission between bacterial cells, which is controlled by signal molecules called self-Inducers. By regulating multiple cellular activities such as pathogenicity, bactericidal tolerance, spore production, neurotoxin generation, locomotion, biofilms generation, and antimicrobial resistance, the QS system renders bacterial cells resistant to hostile environments (47). The lux operon controls quorum sensing, which is observed in both gramme positive and gramme negative bacteria (47). However, the method and AIs participating in the process differ.

In Gram negative bacteria, the gene Lux-I generates the enzyme AHL synthase, which makes AHL (N-acyl Homoserine Lactone). When cell density is low, AHL diffuses out of the cell, and Lux-I remains inactive because it is stimulated by a complex produced by AHL

and a protein generated by the Lux-R gene. The Lux-I gene, on the other hand, exhibits basal expression even when not activated. When cell density is high, the concentration of AHL molecules in the surrounding environment rises, allowing it to diffuse into the cell. AHL forms a complex with the protein generated by the Lux-R gene. This combination subsequently activates the Lux-I gene, accelerating the generation of AHL. Lux-R also creates an enzyme called RNA polymerase, which binds to other structural genes and activates them, resulting in the transcription of enzyme and protein-producing genes. (48)

In gram-positive bacteria, two signaling components - sensor kinase and response regulator - govern quorum sensing (48). The cell generates tiny oligopeptides, which develop into AIP. A transporter is used to move AIP out of. AIP links to the biosensor kinase on the cell membrane of bacteria when it reaches a particular concentration. When AIP binds to sensor kinase, the histidine molecule linked to sensor kinase is phosphorylated. The phosphorylated histidine molecules then transfer the phosphate to the response regulator's Aspartate amino acid. This phosphate-added aspartate response regulator then acts as an inducer, binding to the Lux gene promoter and initiating gene expression.

Quorum Sensing: -

It is the destruction or alteration of signaling molecules by enzymes. It might possibly be signal reception or signal creation that is being blocked. This alters gene regulation and impedes the control of gene expression for antibiotic resistance or biofilm formation.

To suppress quorum sensing, AI molecules are changed by modifying their chemical structure, stopping the gene that produces the AI, or blocking the receptors that initiate the process. Lactonase or Oxidoreductase enzymatic activity can be used to breakdown AHL. Furthermore, enzymes such as adenosylhomocysteine or S-adenosyl cysteine Lux-I prevent the production of AH, hence inhibiting total signal generation (48). Another method is to introduce synthetic AI peptides and Halogenated Furanones that bind to the receptor instead of AHL, so inhibiting the process.

2. **Bacteriocins: -** The evolution and expansion of antibiotic resistance in bacterial infections has become a major public health concern (50).Antimicrobial medications that were formerly highly effective against infections now fail to respond to numerous antibiotics (50). Antibiotics used for therapy typically have broad spectrum activity, which means they target a wide range of microbes, increasing the likelihood of resistance-causing mutations (50).

Bacteriocins are antimicrobial toxins generated by bacteria to boost their chances of survival against other closely related strains (49). The majority of bacteriocins differ from traditional antibiotics in two ways: first, they are produced by means of ribosomes, and second, they have a very restricted killing spectrum (50). Antibiotics' extensive usage has led in the evolution of bacterial resistance to antibiotics over time due to their broad killing range (50). However, if bacteriocins occurred long before antibiotics were discovered, how could they retain their efficacy in a domain which they are continually used? Because bacteriocins are only toxic to strains strongly related to the producing bacteria and change continually, the causing bacteria can keep up with inhibition conferring mutations (50).

3. **Nanotherapy**

More and more people are using nano therapy in treatments, especially as a new phase for infections. Nano therapy is based on nanomaterials. Infections caused by multi drug resistance organisms (MDROs) are a growing source of morbidity and death worldwide. There are typically fewer medications for the treatment of infections brought on by MDROs. These clinical problems highlight the immediate requirement for innovative and more efficient antimicrobial procedures Nanotechnology, which is based on the science of using nanomaterials for nano antibiotics and nanodrug supply chain management,

aids in the reduction of antibiotic resistance (51). Nanoparticles have the capacity to penetrate dangerous microorganism cell walls and disrupt critical biochemical processes, resulting in new antibacterial methods (52). Nanoparticles have been shown to have synergistic antibacterial capabilities with regular antibiotics, which may aid in containing the global disaster caused by antibiotic resistance.

Nanomaterials have one dimension in the scale of nanometer (53). Nanoparticles, in particular, have been shown to have broad-spectrum antibacterial activity against Gram-positive and Gramnegative pathogens. The antibacterial mode of action of NPs is frequently outlined using one of three models: oxidative stress production (54), ionic species generation(55), or non-oxidative mechanisms(56).The three primary processes may all be active at the same time.

According to recent study, the key mechanisms through which nanomaterials exhibit their antimicrobial action are as follows: 1) Rupture of the bacterial cell membrane

ROS generation

Bacterial cell membrane penetration

Interaction with Proteins and nucleic acids is involved in the formation of antimicrobial actions within the cell.

Nanoparticles have the potential to treat infectious disorders caused by MDR bacteria (57). Nanoparticles have showed potential promise as medications due to their particular physical and chemical properties (58). Metal oxide nanoparticles such as CuO and Zinc Oxide have been shown to be toxic to methicillin-resistant staphylococcus aureus as well as Escherichia coli (ZnO). **Types of nanoparticles: -**

NPs are so small that they may be employed for a spectrum of bacteria and human transport, pharmaceutical administration, and controlled release of medications applications. These NPs are often classed as natural, incidental, or synthetic; however, synthetic NPs are the bulk of the time employed in applications. In bacteriological applications, NPs typically include metal complexes and inorganic materials such as Ag, Au, Pt, Zn, Ti, Al, Fe, Ni, Cu, Si, quantum dots, and their oxides such as ZnO, TiO2, Fe3O, CuO, SiO2. substances, and various contents. Carbon-based structures such as liposomes, micelles, fullerenes, carbon nanotubes (CNT), graphene and its derivatives. Types of nanoparticles and their targets are as shown in Table 2. The interaction between synthetic nanoparticles and antibiotics is of great importance, as the density and type of surface properties determine the extent to which bacteria are destroyed. Negatively charged antibiotic functionalized particles have been primarily investigated to enhance the antibacterial activity of nanoconjugates (59). Few microbes such as *Escherichia coli, methicillin-resistant Staphylococcus aureus* were studied using charged nanoparticles (60).

Table -2, different types of nanoparticles and their associated functions

Nanoparticles	Conjugated antibiotic	Target bacteria	Target area	Mode of action
Liposomes	Vancomycin	*Staph. aureus*	Cell membrane	Self-assembly of DNA nanomaterials liposomes dramatically increases Van's loading capacity by acting as a fundamental building component. Vancomycin may be released over an extended period of time and ROS can continuously be produced because to

Nanoparticles	Conjugated antibiotic	Target bacteria	Target area	Mode of action
				bacteria's high absorption capability of Van -DNL by intracellular delivery.(61)
Micelle	Vancomycin, Ciprofloxacin	*E. coli*, *P. aeruginosa*	Cell membrane and cell wall and	Van and CIP-loaded microemulsion function as sensory perceptions lipid nanoparticles inside the infected cell. On desire, target-specific binding mechanisms connect with the bacterial membrane to release substantial quantities of pharmacological conjugate. (62)
Dendrimer	Vancomycin	*Staph. aureus, Methicillinresistant staph. aureus*	Cell membrane	Van's drug loading inside the lipid transporters were used for drug delivery into the cell membrane (63).
Silver	Ampicillin	*P. aeruginosa, V. cholera, E. coli*	Outer layer of cell	The dual antimicrobial actions of Amp and AgNP, caused by approximately 523 units of Amp/AgNP, resulted in a tenfold decrease in the amount of Amp-AgNP conjugated required to kill betalactamase resistant microorganisms. (64).
Gold	Gentamycin	*Staph. aureus*	Outer layer of cell	AuNP adducts bind to the outer membrane, penetrate the organism, and emit a considerable amount of gentamicin. (65).
Gold	Vancomycin	*Vanccomycin-resistant enterococci, E. coli*	Inner bacterial membrane	The bacterial cell membrane is multi- or polyvalently inhibited by van-capped AuNP (66).
CeO2	Beta- lactam (cefotaxime, impenem, amoxicillin, clavulanate, ampicillin)	*K. pneumonia* carbapenemase KPC, *E. coli*	Outer bacterial membrane	Create oxidative stress and enhance the susceptibility of the cell membrane by introducing Ce3+ or Ce4+ particles to the cellular membranes. (67).
Fe3O4	Tobramycin	*P. aeruginosa*	Biofilm`s outer	Alginate-coated Fe3O4 NPs, which have an unusually high negative

Nanoparticles	Conjugated antibiotic	Target bacteria	Target area	Mode of action
			membrane	surface charge, diffuse over the negatively charged biofilm's outer layer. Iron oxide nanoparticles with an alginate coating are quickly bio-absorbed by the biofilm barrier and transport tobramycin to the desired location (68).
Graphene oxide	Tetracycline	*E. coli*	Avoid the efflux pump membrane proteins	Tetracycline enters the cytoplasm via nanographene and links to the ribosome. NGO peptides are larger in size than efflux motor protein molecules. Tetracycline is thus retained within the cell and suppresses bacterial development.(69).
Carbon nanotubes	Tetracycline	*E. coli*	Avoid the efflux pump membrane proteins	The bacterial membrane to be more effectively penetrated by needleshaped SWCNT, which can also more effectively transfer TET further into cytoplasm where it can connect with ribosomes. Due to bigger size of SWCNT than the efflux motor membrane peptides, TET is kept in the bacterial cell, which stops the development of bacteria (69).

Nanomaterial based vaccine: -

Several NPs have demonstrated the ability to elicit immunological responses via a variety of pathways, providing an alternative to the adjuvants and vaccine delivery methods now in use (70). For instance, NPs enable the production of important proteins in the right shape on their surfaces, which helps to precisely trigger an immune response (71,72). To prevent antigens against degrading, NPs are used as delivery mechanisms. In this context, nanoparticles with very well chemical compositions, adjustable structural designs, programmable immunostimulatory capabilities, and sophisticated engineering designs are promising vaccine candidates for successfully preventing and treating pathogenic bacteria (73).

Other technological challenges for effective vaccine development and immunization campaigns include vaccine composition, "cold-chain" preservation, stability, route of administration, and lengthy delivery (74). In this context, it is advisable to use customized nanoparticles with a wide range of evolution, shapes, sizes, surface properties as well as biochemical

processes as ideal delivery methods to protect vaccines and their antigens, enhance epitopes preparation and demonstration, make it simpler for make unique cells called APCs to take up the vaccines and their antigens, and raise vaccine reliability (75).

For example, macrophages preferentially eat anionic particles (76). Chitin and other ionic Nanoparticles are mucoadhesive, enabling them to interact with mucous immune system and remain in mucus for prolonged periods of time (77,78). Furthermore, nanotechnology allow for the improvement of adjuvant action, the reduction of dose by carefully managing the dispersion of epitope or post around or even inside APCs, and the reduction of undesirable effects such as acute infection. Nanotechnology provides an excellent foundation for developing new modern vaccines and facilitating their widespread use. There are a number of vaccines designed using nanomaterials for controlling infections from bacteria that are used by humans and several others are in clinical trials. These vaccines use various nanomaterials such as dendrimers, polyelectrolyte multilayers, polyamides, polymeric materials, polyesters, polymeric materials, and polyesters. Transport and delivery of various peptides, nucleic acids, protein antigens, and drugs are major applications of vaccines (79). Antigens can be encapsulated in NPs or attached to the surface of particles to reach target cells (80,81). NPs can modulate, amplify and enhance epitope density due to their particulate structure, whereas APCs internalize and digest antigens (82). It can also activate the innate immune system. It is important to control the strength and efficacy of the immune response by sequentially delivering many antigens and adjuvants using nanomaterials. They can be fine-tuned to shift immunological polarization in favor of specific subtypes. All these favorable properties of nanoparticles can enhance vaccination coverage and efficacy compared to other standard delivery approaches. In conclusion, the combination of nanoparticles and vaccines is a useful, safe, and effective method for manufacturing AMR vaccines.

Lymphatic drainage is influenced by the physical properties of nanoparticles (83). The transportation of nanoparticles across the mucus layer is helped by hydrophilic polymers (8).

Cationic nanoparticles can also adhere to mucus and contact mucus immune cells. Chitosan has been used in mucosal-administered vaccine NPs containing TB (85). The nanoparticle vaccine enhances adjuvant efficacy and reduces adverse local/systemic effects such as toxicity and inflammation. In addition, several NPs possess unique adjuvant properties triggered by complement, delivery of pro-inflammatory cytokines, or activation of B cells without the need for TLR ligands or other adjuvants (86). These properties are useful as they can reduce toxicity and inflammation caused by other adjuvants while facilitating vaccine production and administration (80).

Essential oils: -

Essential oils are volatile phytochemicals. About 17,500 plant species from various flowering plant families, including the *Labiatae, Rutaceae,* and *Myrtaceae,* produce her EO. However, only about 300 of these are in commercial use (87). The compounds found in essential oils are produced in the cytoplasm and plastids of plant cells via the malonate, mevalonate, and methyl-D-erythritol-

-phosphate pathways. They are dispersed as small droplets in branches, shoots, flowers, fruiting bodies, bark, and plant roots, and are produced and stored in various secretory systems, including ducts, secretory departments, and resin ducts. EOs are primarily constituted of hydrocarbons, terpenes, and phenolics, however, they also comprise two or three other major components at concentrations ranging from 20 to 70%. Other chemicals that may be present include saturated lipids, oxides, and sulfate derivatives [88]. Essential oils (EOs) are utilized in medicine because of their biological qualities, which include inhibitory activities, analgesic, and anti-inflammatory effects, and

anti-oxidant, fungicidal, and anticancer capabilities, among others. Many essential oils have antimicrobial qualities that are useful in business and science, such as beauty, farming, and healthcare.

Antimicrobial resistance is a crucial issue in tackling the fast-growing problem of resistant microorganisms. Six million individuals died globally as a result of infection of respiratory system infections, TB, or diarrheal disorders in 2016. The number of pathogen strains resistant to currently available medicines is also growing. The bacteria strains resistant to antibiotics is also growing. Antibiotic-resistant bacterial infection is more harmful to patients. As per reports from WHO on *Salmonella* agents, quinolone resistance, E. coli resistance to beta-lactam antibiotics, *Staphylococcus aureus* resistance to antibiotic classes, *Streptococcus pneumoniae* resistance to penicillin, and third-generation carbapenems and cephalosporins Inhibition of *Klebsiella pneumoniae* is the most serious problem that is antimicrobial resistance. *Candidiasis* is the most prevalent fungal illness, with over 20 Isolates capable of infecting humans. *Candidiasis* is mostly characterized by Candida. With approximately 20 Candida species able to invade humans, *candidiasis* is the most prevalent skin disease and is caused mostly by *C. albicans*, with *C. glabrata* and *C. parapsilosis* having less severe repercussions [92]. *Aspergillosis,* toxoplasmosis, and epidermal mycosis (commonly known as ringworm) are the most common fungal infections [90].

DIFFERENT TYPES OF ESSENTIAL OILS AND THEIR CONSEQUENCES:

- Lavender essential oil

Lavender essential oil (EO) is used in both traditional medicine and cosmetics. It is thought to have anxiolytic, anti-inflammatory, and antibacterial properties (91). The lavender essential oil has a synergistic effect against beta-lactamase-producing *E. coli* when used with the antibiotic piperacillin [92]. This discovery shows that lavender essential oil may be used to modify resistance to antibiotics. (93) Another study comparing the antibacterial activity of four different types of lavender oil on MRSA infections found that the oil suppresses the growth of these germs when in direct contact [94]. Fusidic acid, one of the components in this oil, is crucial for the antimicrobial effect. It harms bacterial cells by reducing protein synthesis [95].

Cinnamon bark essential oil

The numerous components of the tropical evergreen tree can create cinnamon bark EO, which is helpful to human health [95]. An earlier investigation discovered a synergic effect among cinnamon essential EO and piperacillin, suggesting the potential for cinnamon bark EO to be used as a resistance-modifying medication against MDR bacteria [92,96]. Cinnamaldehyde, one of the compounds in cinnamon essential oil that inhibits the action of amino decarboxylation, and other components contribute to the oil's potential to inhibit some pathogenic microorganisms [97].

Essential oil of peppermint

Whenever piperacillin and peppermint essential oils were mixed, a potential option to lower antibiotic usage and attain reversal beta-lactam antimicrobial resistance was revealed. (98). The antibacterial activity of this oil has been attributed to high levels of camphor and acetone extract [99].

4. PHAGE THERAPY

Antimicrobial agents are manufactured, including commonly used antibiotics such as streptomycin. As a result, the contribution of drugs in disease prevention and treatment has changed. However, Due to the rapid development of antibiotic resistance after synthesis, the production of new antimicrobials is no longer cost-effective (103,104).

Thus, *Escherichia coli, Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa* and *enterococci* were so limited that the development of new antimicrobial-resistant infection treatments was necessary (107). In an era of rising MDR bacteria

growth and a scarcity of new antibiotics, using phage as a non-conventional and biological antibacterial agent provides a novel approach. Bacteriophages can now be used effectively in a variety of contexts, including food quality, agricultural, and animal health implementations, surveillance and management of food contamination, industrial, phage medicinal usage, and clinical testing, such as bacterial identification and genotyping in human infections.

Their bactericidal activity, low intrinsic toxicity, high selectivity, lack of cross-resistance with other types of antibiotics, and ability to grow in host organisms distinguish them from conventional antibiotics. (106,107,100,102,103,105) Furthermore, unlike broad-spectrum antimicrobials, phages protect the commensal flora by strain-specific action, which is especially essential for the elderly and immunocompromised. They will soon be available in powder form, eliminating the need for a cold chain (105). When contrast to pharmaceuticals, phage therapy appears to hold the most promise for the treatment of infectious illnesses in the future. Phages have been used to treat *S. aureus, P. aeruginosa, A. baumannii, and E. faecalis* infections. For the treatment of MDR *S. aureus*-induced chronic rhinosinusitis, Ooi et al. Phage cocktail AB-SA01 is used. Multiple intranasal phage doses led to an effective therapy with minimal adverse effects, indicating that this diagnostic might be used in place of antimicrobial medications (109).

A further study used the contagious bacterial phage Sb-1 to cure diabetics' blisters, and the results showed that topically putting a bacterial mono-phage pair to the ailment may help even if the drug regimen had failed (110). Furthermore, despite the fact that antibiotic treatment was unsuccessful in this case, Chan et al. used phage OMKO1 to cure a P. pseudomonas fluorescens aortic transplant. According to their findings, phage and cefotaxime improved the situation and avoided resurgence. In this study, they employed imaging guidance to reach the Perigraft collection via needle puncture just before the aortic root (111). Another case study revealed that treating P. aeruginosa septic shock in people with injectable phages cocktail BFC1 is successful (112).

Conclusion:

Antibiotic resistance is the most serious concern these days. Patients infected with such resistant bacteria are either ill or on the verge of death. Thus, the strategies explained above are the solution to this problem. Combinational strategies and therapies with nano-targeted approaches are promising techniques to combat this hitch.

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