Combating Multidrug Resistance: The Potential of Antimicrobial Peptides and Biofilm Challenges

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Abstract:- The escalating crisis of antibiotic resistance represents a formidable challenge to global public health, necessitating urgent and innovative solutions. This review delves into the multifaceted nature of antibiotic resistance, emphasizing the pivotal role of biofilms and the genetic mechanisms underpinning resistance in both Gram-positive and Gram-negative bacteria. A significant focus is placed on Staphylococcus aureus, particularly methicillin-resistant S. aureus (MRSA), and its mechanisms of resistance, including the SCCmec element and the agr quorum sensing system. The review also explores the alarming rise of resistance in Gram-negative pathogens, such as *E. coli* and *K. pneumoniae*, highlighting the perilous spread of extended-spectrum β-lactamases (ESBLs) and carbapenemases. Amidst this dire landscape, antimicrobial peptides (AMPs), particularly melittin from bee venom (BV), emerge as promising agents capable of breaching microbial defenses, including those of dormant cells within biofilms, thus offering a potential strategy to circumvent traditional resistance mechanisms.

The review underscores the necessity of understanding bacterial survival strategies, such as biofilm formation and genetic adaptation, to develop effective countermeasures against antibiotic-resistant infections. Through a comprehensive analysis of current challenges and potential solutions, this review calls for a concerted effort to innovate and diversify our antimicrobial arsenal, highlighting the critical role of AMPs in the ongoing battle against multidrug-resistant pathogens. This abstract encapsulates the document's exploration of the complexities of antibiotic resistance, the potential of AMPs like melittin, and the importance of innovative strategies to combat this growing threat.

I. INTRODUCTION

Multiple drug resistant bacteria (MDRB) are one of the biggest challenges to world health and new anti-infectives are required to combat it [1]. MDRB occurs when bacteria are capable of surviving in the administration of medications that would typically prevent their development [2]. Quick bacterial protection from anti-microbe treatment is a disturbing part of the fundamental disease, which can advance rapidly without powerful treatment [3].

Therefore, the increasing resistance of most clinically relevant bacteria to antibiotics creates an immediate need for new classes of anti-bacteria that are not impacted by the microbiological populace's existing resistance mechanisms [4].

In many circumstances, illnesses caused by resistant microorganisms would increase expenditures for the patient and the healthcare system. Antibiotics used as a last option are occasionally more costly and harder to get [5]. Assessments of the possible financial impact of antimicrobial resistance (AMR) from the latest research "The Review on Antimicrobial Resistance" [6], Policymakers are utilizing them to push AMR up the political priority [7]. Health economic models analyzing strategies to treat, prevent, or limit the spread of resistant infections are being used to influence policies. In order to get a more accurate picture of the AMR burden [8, 9].

The most crucial virulence factor that plays a considerable role in antibiotic resistance is biofilm formation, which is described as a sessile microbial community in which cells are connected and integrated into a protective, extracellular polymeric matrix with a surface or other cell [10, 11]. This nature of multiplication has changed the physiology of gene expression and protein manufacturing [10,11]. Bacterial biofilms are inherently resistant to antibiotics because (i) some antibiotics do not penetrate the depth of the biofilm, (ii) some biofilm cells grow slowly or non-grow, probably because of nutrient limitations, and (iii) certain biofilm cells may adopt a protected and separate biofilm phenotype [12]. Biofilm growth serves as a defense against numerous clearance systems during infection [11]. The biofilm matrix can hinder certain immunological defenses, like macrophages that show unfinished entry into the biofilm matrix and "frustrated phagocytosis" [13]. Furthermore, biofilm cells have increased antibiotic endurance [14]. Also, biofilms perform a key position in chronic disease progression [11]. After a biofilm has been

established, separate cells can spread from the initial biofilm and either seed afresh sight of infection or arbitrate an acute infection like sepsis [12].

The emergence of drug-resistant microorganisms and the resistance of key bacterial pathogens to standard antimicrobial medicines is worrying. There are difficulties in the fight against bacterial infections and accompanying diseases and the current lack of effective drugs, lack of successful preventive measures, and only a few new antibiotics in the medical pipeline will require new treatment options and alternative antimicrobial treatments to be developed [15].

MDRB has been put forward several approaches to solving it, but the development of new natural antimicrobial agents is the most significant. Therefore, intensive research has focused on developing new approaches to prevent and treat MDR-infection [16].

In addition, anti-infective substances are needed that act through new mechanisms of action [17]. In efforts to identify bioactive compounds, plants offer a promising source of natural components [18]. Research into anti-mechanisms of action may open new opportunities for the development of drugs to fight antibiotic resistance [17], and natural products can serve as a serious reservoir of antibacterial adjuvants to defeat mechanisms of resistance [19].

Many academics studied how chitosan may be used to preserve food as part of the development of natural antimicrobials with animal origins. Currently, in some Asian countries, chitosan has been accepted as the functional food in countries such as Japan and Korea in the last decade [20].

Chitosan, it is a natural biopolymer derived from the exoskeletons of crustaceans and arthropods, regarded for its unique polycational nature, and it was used as an active component for this purpose antimicrobial activity [21].

Chitosan has shown promise for use as an antimicrobial, antioxidant, clarifying agent, and as a packaging material and has acquired a status as a potential promising alternative as a natural antibacterial [22, 23]. Therefore, the objective of the current study is isolation of the most multidrug resistant bacterial strains, with an attempt to overcome these resistant microorganisms via screening of the antibacterial and anti-biofilm activities of five medicinal plants named *Nigella sativa*, *Ziziphus spina-christi*, *Rosmarinus officinalis*, *Origanum majorana*, and *Allium sativum,* as well as chitosan on isolated MDRB.

II. LITERATUTER REVIEW

A. Antibiotic Resistance

The capacity of microorganisms to exchange in approaches that face up to the consequences of drugs – "that is, the germs didn't die, and their augmentation is now not come to a stop" called antibiotic resistance [24].When bacteria are confronted with antibiotics, the progression of resistance occurs automatically Nevertheless, antibiotic

overuse hastens the procedure, and a variety of variables can influence its progression [25].

SIR system standard Infection Ratio) is categorized as bacterial spices in medical terms the effects of almost genetic alterations which raise a strain's MIC above the epidemiologic breakpoint are referred to as developing resistance. Contrarily, clinical resistance describes the effects of insertional mutagenesis that cause a strain's MIC to rise just above point at where it is easily cured by conventional medication [26].

S = sensitive (MIC below therapeutic borderline, it is effective with routine medication); I = intermediate; R = resist (MIC high therapeutic borderline, it is not effective with routine medication).

Resistance to antimicrobials in pathogenic bacteria is a global challenge linked to high mortality rates [27]. Multidrug-resistant in both Gram-positive and negative bacteria have resulted in infections that are hard to treat or untreated with classic antimicrobial agents. Due to the late identification of pathogens and their antibacterial susceptibility. Among numerous hospitalized persons who suffering from bacteremia and other severe illnesses, a wide range of antibiotics are widely used liberally and needlessly [27]. There are dramatic increases in the development of resistance occurring then, when associated with weak disease prevention methods, The surroundings as well as other patients are easily exposed to resistant microorganisms [27]. The availability of improved epidemiological data on anti-bacterial resistance in commonly encountered pathogenic bacteria will be effective not only for decision-making on treatment strategies, but also for the development of an appropriate antimicrobial management programmed in hospitals [27]. Vital pathogenic bacteria are increasingly becoming resistant to basic antibiotic treatments, and the emergence of multidrug-resistant bacteria is concerning. There are obstacles in the struggle towards bacterial infections and the associated diseases, and the current dearth of efficient treatments, the failure of preventive measures, and the small number of new antibiotics in development will necessitate the development of alternative antimicrobial remedies [15].

Among harmful bacteria, the growth and development of antimicrobial agents has become an increasing issue for public healthcare in latest years.

All pathogenic, commensal, and environmental bacteria, mobile genetical elements, and bacteriophages comprise an ARG (resistome) reservoir from which pathogens could develop resistance through horizontal gene transmission (HGT) [28].

The propagation of resistant strains from commensalism and ambient microbes to harmful types has been facilitated by HGT, as certain clinically significant ARGs have demonstrated. While transformation and transduction are regarded as less crucial, recent studies indicate that their involvement may be more substantial than

previously thought. Understanding the extent of the resistance and how it mobilizes against pathogenic bacteria is necessary for efforts to limit the spread of those genes. The authors discussed the resistant concept, providing examples of HGT of clinically relevant ARGs and a summary of current knowledge of the contributions made by different HGT mechanisms to the spread of resistance to antibiotics [28].

Multi-drug-resistant pathogens have risen over recent decades and cause severe problems [29]. Resistant bacterial infections have contributed to mortality and morbidity, and treatments are urgently needed to fight bacterial resistance [28].

The WHO's most recent and first worldwide assessment on drug resistance, issued in April 2014, shows disturbingly high rates of drug resistance in the bacteria that commonly lead to illnesses in hospitals and the society. *E. coli, MRSA, and K. pneumoniae* have major interest. *E. coli is* resistant to fluoroquinolones, *K. pneumoniae* is resistant to carbapenems, and both of them tolerant to third generation of cephalosporin's. E. coli is widespread in both humans and animals' normal gut flora. Despite this, it is the main cause of healthcare and community-acquired UTIS, septicemia, and foodborne infections worldwide. An excessive incidence of resisting *E. coli* to antibiotics has been pronounced [30].

It was found that the resistance attributed to the third generation of cephalosporin's to *E. coli* that causes many diseases through a blood test in an Indian hospital was estimated at 86% [31].

Long-lasting sickness and a high fatality rate are caused by resistance to antibiotics. It is predicted that every year, diseases for which there are no efficient medications result in the death of more than 200,000 neonates [32]. The state's health care institutions will incur heavy expenses as a result of the high resistance to antibiotics, in addition individuals. Newly antibiotics are frequently greater cost and much less reachable.

[30, 33] People who suffer from infection which highly resist to antibiotic, in India have to payment around 700 USD more than who suffering from infectious diseases treatable with first line antibiotics .it is estimated more than a year's earnings for Indian rustic laborer [33]. Since resources are scarce and the prevalence of communicable diseases is significantly greater, bacterial infection is particularly destructive in low- and middle-income countries (LMICs). In these nations, it is also challenging for infection measures for prevention and management to be successful [34].

Once upon a time, an elevated incidence of resistance was discovered in all pattern sources. Among *E. coli* isolates from kid's feces microflora, it was discovered that there was 92 percent tolerance to at minimum one of the tested antibiotics and 24 percent multi-drug resistance. An earlier examination on *E. coli* from healthful child's feces was conducted in Tamil Naduand India, in 2005. found 63% resistance to at least one antibiotic and 32% multi resistance [35].

According to 1998 research in Greece, 40% of toddlers in good health have conferring resistance *E. coli* [36]. In Vietnam, there was also a significant prevalence of tolerance in commensal *E. coli* among kids [37]. Ecological pollution with pathogenic bacteria strongly shares the antibiotic resistance spreading in *Escherichia coli* amongst Peruvian youngsters [38]. Among the *E. coli* isolated from cow-dung, 19% were found to be multi-resistant, despite the fact that participants were informed that just 5% of cows had been treated with antibiotics.

Antibiotic resistance develops in commensal *E. coli* isolates from farm cow feces, as a result of veterinary antibiotic usage [39].

In a previous study in the United States, *E. coli* isolates from cow manure from healthy nursing cows were shown to have 40% multidrug resistance [40]. *E. coli* strains which isolated from drinkable water samples were shown to be multi-resistant in 24 percent of cases. 8 that out 9 tap water samples collected from the Indian Subcontinent's *E. coli* bacteria were discovered in a prior study to really be susceptible to at least one testing antibiotic [35], 63 percent of the *E. coli* specimens from drinkable water in research from Hyderabad, Pakistan, were multi-resistant [41]. Emerging pathogens in drinking water are becoming more of a concern [42], and antibiotic resistant bacteria have been found in the aquatic environment [43]. Bacterial, harmful, and/or resistant strains of bacteria identification in water is widespread in nations such as India, wherein water resources are easily contaminated due to unclean sanitation practices.

Both the water and the ground ecology are home to antibiotic-resistant microorganisms [44]. It was also found in animal and human resources E. coli which resistant to antibiotics [45]. The choice of antibiotic-resistant microorganisms at extremely low antibiotic concentrations has also been reported [46]. A previous study in Virginia, USA, demonstrated the presence of fecal contamination in pastoral areas, water is a harbor of microorganisms that are unable to be eradicated [47]. Due to the lack of proper sanitary amenities in 80 percent of the homeowners mostly in research project, defecation in open areas activities were used. These activities may also have extended antibiotic residues and resistant bacteria in the aqua cultural and grasses ecosystems, where run-off water could then transport them to freshwater resources.

B. Multi Drug Resistance Bacteria (MDRB)

Due to resistance's evolution into MDRB, the progression of resistance throughout many different diseases has reached previously unheard-of levels. As a consequence, both mortality rates and morbidity have grown globally, and we face a future post-antibiotic period today [30]. Strains of bacteria from the ESKAPE pathogen category, in particular (*E. faecium, S. aureus, K. pneumoniae, Acinetobacter, P. aeruginosa, and Enterobacter*) are of importance to this pandemic [48]. These pathogens, which include both Gram-negative organisms and Gram-positive pathogens, frequently possess MDRB-determining genes that reside on genetic resistance islands (RI) of complicated evolutionary history

that were already coded on chromosomes or plasmids [49, 50]. The majority of discovered pathogens in angioplasty infectious diseases originated from human epidermis and healthcare facilities: *Staph.spp* [51, 52], *Streptococcus* spp [53], *Pseudomonas* spp. [54, 55].

➢ *MDR Gram-Positive Bacteria*

The prevalence of MDR in Gram-positive microbes is shown through the significant bacterium *Staphylococcus aureus*, an opportunist one. Approximately 30% of people carry this bacterial as a typical symbiont [56]. Numerous illnesses are brought on by the microbe, ranging from skin infections to cardiomyopathy, which can be fatal [57]. 80% of those who contracted septicemia from S. aureus before the invention of penicillin died [56]. Penicillin discovery resulted in major usage against *S. aureus*. By the mid-1940s penicillin resistance was prevalent because of plasmid-borne penicillinases [58]. In 1959, semi-synthetic penicillin (methicillin), which was resistant to bio degradation, was approved for use as an alternate therapy. In England, methicillin-resistant *Staphylococcus aureus (MRSA)* had been identified by 1961 [58].

The *MRSA* genotypes are characterized by the presence of the SCCmec component staphylococcus cassette methicillin resistant gene, of which 11 kinds have been identified [56]. The SCCmec components all have the following characteristics: i) they all inserted into the same location on the S. aureus chromosome as the orfX gene. ii) They have a mecA gene (PBP2a) that is regulated by mecI and mecR regulatory genes, as well as the cassette chromosomal recombinase (ccr), which mediated the SCCmec component's excision and integration., iii) resection and integrations are mediated by the ccr-encoded DNA recombinase's identification of the inserting site sequence located within particular inverted and direct repetitions [56].

MRSA isolates arose from a previous curable background of methicillin-sensitive Staphy*lococcus aureus* (*MSSA*). Since then, other *MRSA* lineages have emerged, and they are now classified into three primary groups: community-associated *MRSA* (*CAMRSA*), healthcare-associated *MRSA* (*HA-MRSA*) and most recently, livestock-associated *MRSA* (*LA-MRSA*) [58, 59] While they all have the SCCmec cassette, which makes them resistant to almost all β-lactam antibiotics, they vary in their capacity to induce infection. Both *HA-MRSA* and *LA-MRSA* have been proven to produce nosocomial infections in hospitalized patients [59, 60], while *LA-MRSA* is regarded less aggressive in humans [58].

In contrast to newly discovered *CA-MRSA* strains like USA300, which are able to infect otherwise healthy people [61, 62] The variations across MRSA lineages are mostly due to variations in virulence between samples from various lineages. *MSSA* isolate and *MRSA* virulence is based on a number of mechanisms, including toxin generation, cell adhesion characteristics, and immune evasion, to mention a few [59].

Strains of *MRSA* are hazardous because, in addition to their SCCmec genotype, they frequently possess resistance genes to other essential antibiotics used to treat *S. aureus* infections. Due to enzymatic breakdown or antibiotic modification, resistance to aminoglycosides has been reported in up to 70% of *MRSA* isolates in Europe [63]. Because of these considerations, vancomycins and oxazolidinones are the therapy of choice for *MRSA*.Vancomycin resistant has indeed been described as intermittently vancomycin resistance *Staph. aureus* (VISA) [64] or as vancomycin resistant *S. aureus* (VRSA) [65].

Moreover, vancomycin resistance has been documented by horizontal gene transfer of the vanA gene cluster, which comes from another major Gram-positive bacterium, vancomycin-resistant Enterococcus faecalis (VRE) [66, 67]. On the peptidoglycan precursors Lipid-II, a ligase known as VanA is tasked with generating an alternative penta peptide within which the dipeptide (D-Ala-DAla) is switched out for D-Ala-D-Lac, altering the selectivity of vancomycin [67]. The VanS-VanR two-component system, initially identified in E. faecium, controls the induction of the vanA gene cluster in response to exogenous glycopeptide [68]. VanS (sensor kinase) detects extracellular vancomycin when it binds to D-Ala-D-Ala and VanS phosphorylates enzyme the response regulator (VanR) which in turn regulate expression of the vanHAX genes responsible for the D-Ala-D-Lac dipeptide substitution [68], such as linezolid.

Linezolid is increasingly being utilized as a therapy for MRSA, as well as for VRE [70] and resistance evolution is thought to be improbable.

This is owing to the synthetic composition of the molecule, which makes enzymatic breakdown by naturally occurring enzymes improbable [71].

Linezolid also targets and binds to the 23S rRNA of the 50S ribosomal subunit, which is encoded in many copies in the ribosomal DNA (rDNA) genes. Resistance through mutation should be slowed as a result of this [71]. Linezolid resistance is uncommon [72], But it has been linked to mutations in several 23S rRNA genes. There has been no evidence of cross resistance to other protein synthesis inhibitors due to mutations [73]. The presence of a Cfr rRNA methyl transferase, which adds a methyl group to the 23S rRNA at base position A2503, has been linked to further linezolid resistance [74].

The current last-resort antibiotic is used to treat severe VISA, VRSA, VRE, and vancomycin-resistant *E. faecium*. To treat *E. faecium* that is resistant to vancomycin, the lipopeptide antibiotic daptomycin is indicated. Daptomycin interacts with the bacterial membrane via electrostatic interactions, which are Ca^{2+} and phosphatidylglycerol (PG) dependent [76, 77]. As a result, the membrane becomes unstable, and cell division proteins become mis-localized [77].

In VISA isolates with overlapped crossing resistant to vancomycin's, resistance to daptomycin has also been detected via hardening of the bacterial cell [78] or by alterations to genes such as the mprF gene, which encodes the MprF protein (lysylphosphatidyl glycerol synthetase). This gene's malfunctioning regulation allows for the production of lysyl-phosphatidylglycerol (L-PG) rather than the usual PG, altering the total net charge of the bacterial cell membrane Figure (1) [79].
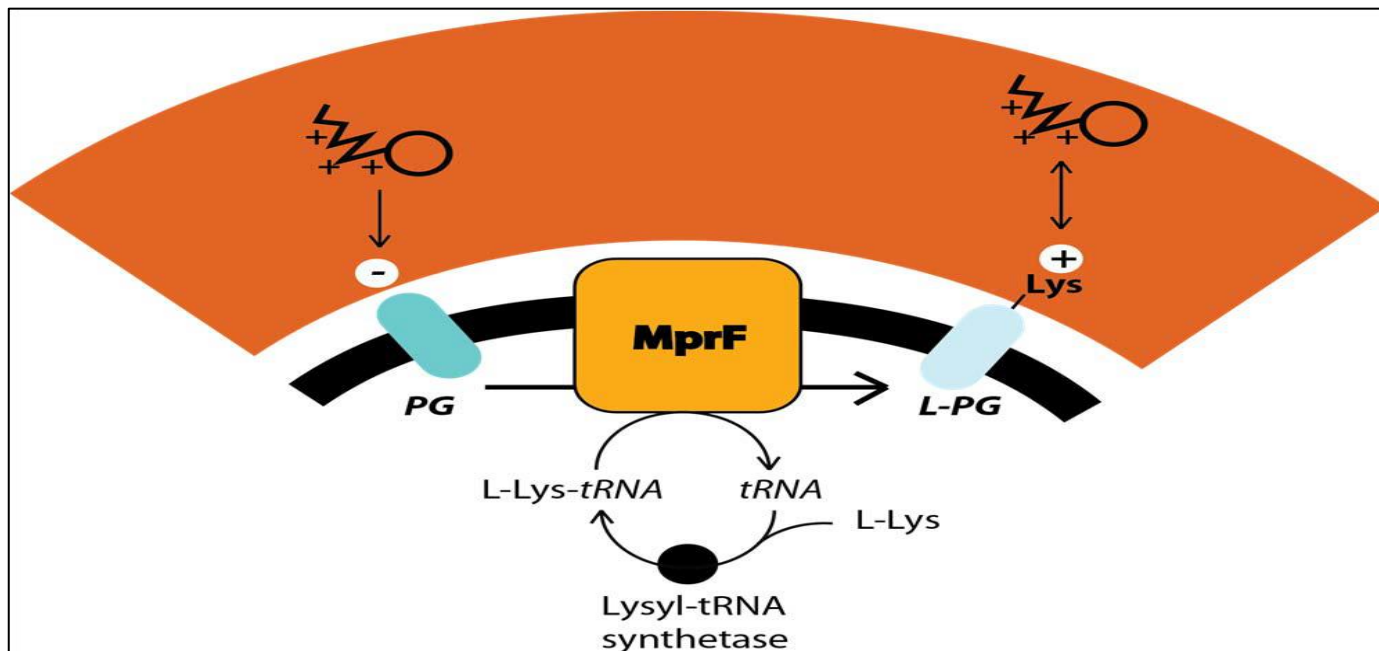

Fig 1: Lysyl Phosphatidyl Glycerol (L-PG) Synthesis: Adapted from (Staubitz *et al.*, 2004) the Staphylococcal Cell Wall with Peptidoglycan (Orange) and Underlying Negatively Charged Phosphatidylglycerol (PG) Containing Membrane (Black). Dysfunctional Expression of the MprF Protein Facilitates Synthesis of Lysyl Phosphatidyl Glycerol (L-PG). L-Lysine is Believed to be Derived from Lysyl-tRNA. L-PG Renders the Bacterium Resistant to Daptomycin and other Electrostatic Interacting Antimicrobials Such as Host Innate Immune Defense Peptides like Defensins.

Because resistant isolates are constantly being developed and disseminated, it is critical to find new tactics for tackling key Gram-positive bacteria. While antibiotics for MRSA in the UK [79], there is still a need to find new or better medicines for Gram-positive infections. Telavancin, the most recent antibiotic for severe Gram-positive infections, is a derivative of the previously established antibiotic vancomycin, as have so many other medicines [80].

➤ *MDR Gram-Negative Bacteria*

Multidrug resistance (MDR) Gram-negative bacterial pathogens are, by far, the most significant and costly in today's society, since MDR Gram-negative infections cause the great majority of nosocomial infections [81]. The extended spectrum is carried by the most troublesome strains. β-Lactamase.

These encode β-Lactamase enzymes with the capacity to hydrolyze several generations of the β-Lactam antibiotics such as penicillins, cephalosporins and, the last resort β-lactams, the carbapenems [82, 83]. Enterobacteria with the CTX-M-15 (ESBL) gene, such as *E. coli* sequence type ST131 [84] and *K. pneumoniae* carbapenemase (KPC) ST258 strain, are important bacterial strains [83, 85]. Several ESBL enzyme inhibitors, such as tazobactam and clavulanic acid [86], have been discovered; however, resistance to such inhibitors has been observed in *E coli* [87].

P. aeruginosa and A. baumannii are two more very significant MDR Gram-negative bacteria [88]. *A. baumannii* is a relatively recent issue in hospital settings, but it is becoming a significant problem among immunocompromised individuals [89]. It is the cause of a wide range of diseases, including skin and soft tissue infections, UTI, and life-threatening pneumonias [90]. Because *A. baumannii* is a less frequent cause of serious infection compared to MDR *E. coli, K. pneumoniae* and *P. aeruginosa,* it is often misdiagnosed and the success of initial antimicrobial therapy against *A. baumannii* is compromised [91].

A. baumannii has recently become a major nosocomial infection largamente due to its capacity to acquire gene determination resistance and its adaptation to environmentally friendly conditions [88]. The AYE strain shows how *A. baumannii* may acquire resistance genes described by [92]. An 86-kilobase resistance island in this strain with resistance to a variety of β-lactams, fluoroquinolones, tetracycline's, aminoglycosides, and other antibiotics. The horizontal gene transfer method was used to acquire the majority of the genes [92]. Other Gram-negative bacteria, such as *K. pneumoniae*, have been linked to widespread MDR tolerance, particularly the spreading of ESBL and carbapenemase gene [49].

Because of carbapenemase tolerance, the peptide antibiotics colistin (polymyxin E) and polymyxin B have been reintroduced. Polymyxin E was discovered in 1949, however its application has been restricted to its unappealing toxicity profile [93]. Antimicrobial peptides are now only employed as a last resort against MDR Gram-negative infections that have become resistant to all other antibiotics [93]. As a result, optimal dosage, pharmacokinetics, and pharmacodynamics are less well understood according to FDA and EMA [94].

Polymyxins are cationic amphipathic circular peptides that cause bacterial membrane rupture. Specifically, polymyxins disrupt membrane integrity via electrostatic interaction with the anionic charged LPS (lipo poly saccharide) layer of the outer membrane while displacing Mg^{2+} and Ca^{2+}, leading to cell leakage and cell lysis [95].

Colistin resistance has historically been thought to be unlikely. However, genomic colistin resistance in *A. baumannii and K. pneumoniae* has been documented as alterations to the LPS layer [96]. *A. baumannii* colistin tolerance acquired either via complete LPS loss [97] or through alterations in the two-component polymyxin resistance A and B system (PmrA-PmrB).

The two-component PmrA-PmrB system is a vital regulator of LPS altering gene products. External signals, such as low pH, high Fe^{3+}, or Al^{3+}, generally cause PmrA-PmrB to be activated. PmrB, the sensor kinase, auto-phosphorylates and transfers the phosphoryl group to PmrA, the response regulator, when it is triggered. Via DNA binding, phosphorylated PmrA controls LPS altering genes [98].

Colistin resistance through mutations in PmrA-PmrB is mediated via point mutations in pmrB [99], constitutive activation of PmrA [100] or upregulation of pmrAB [99]. These changes can lead to addition of phosphoethanolamine to Lipid A through expression of the pmrC gene [98].

In *K. pneumoniae*, resistance can also be mediated through changes in the PhoP-PhoQ (nonspecific acid phosphatase) two component system [101], which is involved in sensing of Mg^{2+} and Ca^{2+} and which can cross talk through the PmrA-PmrB two component system [102]. Further, PhoP-PhoQ has been shown to regulate the *Pagp* gene responsible for modification of lipid A thereby changing the overall negative charge of the membrane [103]. The innermost portion of LPS, lipid A, anchors it to the bacterial outer membrane. The novel finding of plasmid-mediated colistin resistance in *E. coli*, encoded in the mcr-1 gene, which results in the insertion of phosphoethanol amine to Lipid A, rendering the bacterium colistin resistant, is of paramount relevance [104]. This mechanism is essentially the same as in *A. baumannii* PmrA-PmrB mutants [99].

The development of colistin resistance by horizontal transmission genes highlights the looming threat of an antibiotic-free future. The addition of the mcr-1 gene to Gram-negative bacteria that already have MDR carbapenemase could render them incurable. The rapid onset and spread of the global MDR epidemic have already been attributed to horizontal gene transfer, as previously stated [105]. Colistin resistance will likely rise as a result. As a result, the ongoing pursuit of new or enhanced antibacterial is critical, particularly versus Gram-negative microorganisms of the ESKAPE category [94].

C. Causes of Antibiotic Resistance

There are indications of tolerance throughout every family of pathogens and every category of medications. Consequence, the proliferation of multidrug-resistant pathogens continues to increase throughout many countries, particularly the United States and Europe and the emergence of antibiotic resistance appears to be all but unavoidable. The issue of antibiotic-resistant bacteria is much more severe in various locations around the world in which there lax and widespread restrictions governing antibiotic abuse and overuse. Antibiotic intake is extremely high in intermediate nations, and resistant microbes have become increasingly common in recent decades as a consequence of extensive misuse and overuse of antibiotics, which seem to be frequently ineffective [106]. Antimicrobials are commonly accessible OTC, as well as in nations with stricter regulations, agriculture practices allow for the consumption of antibacterial agents for uses other than treating or preventing microbe's infections that affect humans. As a result, the amount of antibiotic treatment released into the environment remain exceedingly high [107].

Most bacteria like *E. coli* and *S. aureus* contain a single circular chromosome (plasmid) [49, 108]. Exceptions to this do exist, as *V. cholera* has two chromosomes [109] and *B. cepacia* has three [110]. Bacteria are an intricate part of human biology as normal commensals of our intestinal and skin flora [111] Whereas most microbes are beneficial to our overall health, others have evolved into harmful species or are highly infectious, making them antibiotic targets [56, 112]. Bacteria have extremely fast growth times and are abundant in nature. As a result, these species' evolutionary adaptability is genuinely astonishing, which is why resistance development is a persistent issue.

The genetic makeup of all species is crucial in the process of evolution, and mutations to the DNA will accommodate fitness gains, fitness losses, or be neutral [113]. Changes in genetic makeup can alter the amino acid content of antibiotic target proteins, compromising the antibiotic's interaction with its target. As a result, changes to DNA play a critical role in evolutionary processes. Point mutations, insertions, or deletions of single or multiple bases in DNA are typically regarded as small and have little impact on resistance development and spread.

Major DNA rearrangements, such as gene duplication/deletion, homologous or non-homologous recombination, or inversions of chromosomal sections, have a far greater impact on developing resistance [105, 114].

What truly sets bacteria apart from higher organisms is their unprecedented ability to acquire new genetic material either as addition to their genomes or in the form of extrachromosomal genetic material such as plasmids via horizontal gene transfer (Figure 2) [105, 115]. Consumption of free DNA from the environment (transformation through natural competence), phage transduction or conjugation (transfer of DNA or plasmids between bacteria) are all options for acquiring additional genetic material through horizontal gene transfer [115]. The ability to integrate acquired material on the chromosome or plasmid through integrins or transposons is particularly important for these processes [105]. Acquired genes can then be passed to daughter cells by vertical gene transfer or passed on to other species via horizontal gene transfer (Figure 2), [115].
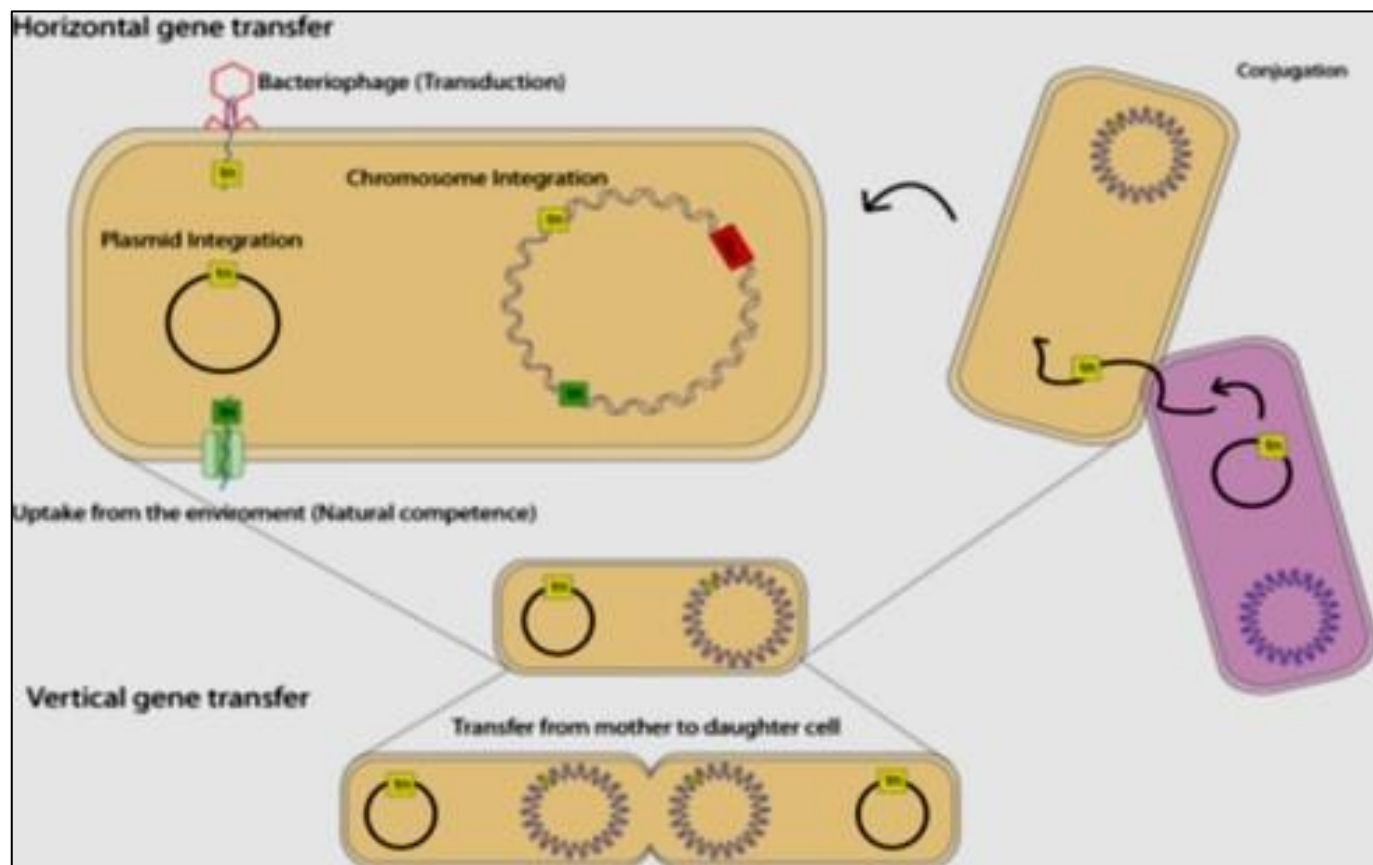

Fig 2: Vertical and Horizontal Gene Transfer: Adapted from Horizontal Gene Transfer can Occur by Phage Transduction, Natural Competence (Acquisition of DNA from the Environment), or Conjugation (here Exemplified by Plasmid Transfer from One Species to Another). As Shown Below, Integrons and Transposons (tn) can Introduce Genetic Material into DNA/Plasmids. Vertical Gene Transfers or Horizontal Gene Transfers are used to pass on Genes and Mutations to the Next Generation [115].

D. Mechanisms of Antibiotic Resistance

Defense techniques by pathogens bacteria either innate or acquired by contact with a different micro-organism, exposure to a new environment condition, or antibiotic [116]. Certain microorganisms are inherently resistant to one or even more types of antimicrobial agents. Naturally resistant microorganisms can occasionally be found in environments in which this isn't the main objective. For instance, several insect's intestinal biomes that haven't been exposed to medicines include efflux pumps which give *E. coli* antibiotic resistance [117]. The public health field is concerned with acquired resistance because once effective antibiotics become ineffective [61]. Since potent pharmaceuticals eventually lose their effectiveness, acquired resistance would be a challenge in the realm of public healthcare [116]. Horizontal DNA fragment absorption by a recipient bacterium, which results in the recipient cell's recombining with the donor cell to produce a recumbent cell, is known as transformation. Conjugation, also known as whole-chromosome or plasmid transference, would be the process by which foreign DNA is transferred from one bacterium to another by direct connection. Transmission of genetic material by bacteriophages is called transduction [111].

There are two basic ways for bacteria to gain acquired antibiotic resistance, in addition to intrinsic resistance: horizontal transmission transfer or spontaneously *de novo* chromosomal changes. Acquired resistance differs from intrinsic resistance in that it is learned rather than inherited (HGT). Chromosome mutagens independently of environmental stimuli, but the transition of outside genetic information via the pathways of transformation, transduction, or conjugation requires direct interaction between both the etiological agent and DNA-containing microbes that serve as the origin of the resistance genes. The non-pathogenic micro biosphere may be the location of the source of the resistance genes that are passed on to human pathogens via HGT, as already noted [107].

Depending on the fluoroquinolone (ex. Ciprofloxacin) and bacterial strain, DNA gyrase is a goal of fluoroquinolones in Gram-negative bacteria, and fluoroquinolone resistance is mediated through mutations in the parC and parE genes as well as the gyrA and gyrB genes (topoisomerase IV genes, primarily target of fluoroquinolones in Gram-positive bacteria) [118]. This mechanism of defense can be handled by carrying alternate copies of the target protein that are inducible when required and allow the bacteria to survive. SCCmec (staphylococcal cassette chromosome mec) is consider mobile genetic of *MRSA* containing the mecA gene encoding an alternate penicillin binding protein (PBP2a) activated by β -lactams and with low affinity for β-lactam drugs [119].

Horizontal gene transfer (HGT) is used to obtain acquired mechanisms of resistance, which include plasmid-encoded specialized efflux pumps (such as TetK and TetL of S. aureus). and enzymes capable of altering the antibiotic or the drug's target [120].

Because resistance determinants are now plasmid-mediated rather than chromosomal, these routes pose a larger threat to humans [121, 122]

Efflux, influx, or a mixture of these characteristics impart resistance. Resistance mechanisms continue to target by-pass systems [19]. Efflux pumps, for example, can convey resistance to numerous antibiotics. In fact, chromosomal modifications of enzymes like β-lactamases are more common than those that are mediated by plasmids [116]. Changing the biosynthesis of the cell wall makes this change successful [61]. An illustration of a pathway alteration that depends on a mutation is altering an already-existing target. One such instance is the mutant of the S12 protein, which makes the 30S component of the ribosomal resistant to streptomycin by changing an only single amino acid [116].

As observed in MRSA, a target by-pass system involves resistance without point alteration but rather the inclusion of a process [116]. Co-selection of antibiotic-resistant microorganisms in connection to minerals and biocontrol, in addition to interconnections between various bacterial resistance, are additional issues with resistance to antibiotics. Minerals and biocontrol both contribute to the rise in resistance to antibiotics by acting as selectable agents. Numerous investigations have confirmed these phenomena, included [123] that shown the structure and function analogies amongst metallic ions and antibiotics, including the efflux systems maintained by both zinc and copper in addition to tetracyclines and β-lactams [124], An even more current findings investigated sequencing genome reported to include AMR and metallic and pesticide resistance in a bid to better comprehend that co-selection. The researchers discovered that germs with metals and pesticide resistance conveyed AMR more frequently than germs without them [125] According to studies, certain sorts of biocide resistance could provide cross-protection in some organisms. Antibacterial agent and biocide cross-resistance in *E. coli* were observed. According to **NCCLS** standards [126] on antibiotic susceptibility tests, cross-resistance

expressed changed strains from "sensitive" to "tolerant" [127]. In terms of fitness, resistance is regarded to have a cost. Commensal pathogens that are not resistant to antibiotics, particularly after antibiotic therapy, may outcompete pathogenic strains or, at the very least, restrain the proliferation of resistant strains. The first analysis was done by **Platt *et al.*** [128] their observation of dairy cows lends credence to this idea. Chlortetracycline in feed greatly boosted transitory tetracycline resistance but decreased the likelihood of recovering ceftiofur-resistant (β-lactam) isolates of *E. coli*.

Typically, efflux is facilitated via molecule-specific or multidrug non-specific antibiotic extrusion over the membrane via passive or active transport [129].

Resistance via efflux is a major issue in antimicrobial and treatment for cancer, however in bacteria, transporters are mostly of the passive variety [119]. The major facilitator family (MF), the ATP-binding cassette (ABC) family, the resistance-nodulating division (RND), the drug/metabolite transporter (DMT) family, and the multidrug and toxic compound extrusion (MATE) family are the five primary families of transporters found in bacteria [129]. Nonspecific multidrug resistance determinants are frequently chromosomal encoded and were probably not designed for drug transport evolutionarily. Whereas efflux of antibiotics by drug specific transporters and often found on plasmids [129].

Chloramphenicol resistance can be accommodated by carriage of the gene (*cmlA*) encoding a protein transporter (MF family) that accommodates efflux of chloramphenicol [130]. In *S. enterica,* multidrug resistance to quinolones, chloramphenicol, and tetracyclines has been shown to be mediated through overexpression of AcrAB-TolC (RND transporter) [131]. Interestingly, increasing the permeability of the membrane can potentially mediate resistance by reducing antibiotic availability. In the Gram-negative Bacterium *P. aeruginosa*, imipenem sensitivity is mediated by multiple mechanisms, one of which is the loss of the outer membrane porin, OprD [132]. Similarly, in the Gram-positive Bacterium *S. aureus*, heightened tolerance to vancomycin can be mediated by cell thickening, as first noticed by **Hiramatsu *et al.*** [63]

Aminoglycoside susceptibility is also mediated by enzymes that change aminoglycosides, such as acetyltransferase (AAC), adenylyl transferases (ANT), or phosphotransferases (APH) [133].

These techniques include avoiding or using an alternative drug-resistant target in place of the targeted treatment [67].

Horizontal gene acquisition leads to the production of enzymes that alter or disintegrate a variety of drugs, leaving them useless fighting pathogens. These enzymes, which have the ability to cleave the β-lactam backbone and play a major role in the development of β-lactam antibiotic resistance, include many carbapenemases and β-lactamases. Enzymes

that change macrolides, aminoglycosides, and a particular variant of an aminoglycoside-modifying enzyme that changes ciprofloxacin [134-136].

Another theory is that there have been genetic modifications that have decreased the quantity of medications which may accomplish the goal and have led to resistant [137] additionally to Pseudomonas's multidrug resistance [138]. Contrarily, changes to porins or other aspects of the cell wall or membrane might limit medication entrance into the cell [139].

Indeed, relative fitness has been assessed for a variety of species and for resistance to various antibiotics via distinct mechanisms. Numerous occurrences of fitness costs associated with resistance mutations have been documented [140]. The likelihood that limiting antibiotic usage will aid in the decline of resistant pathogens is increased by the fact that low-fitness antibiotic-resistant variations should face a massive loss in lack of antibiotic selecting. Nevertheless, epidemiologic analyses of clinically resistant populations and lab evolutionary investigations demonstrated that somehow this prediction is readily misguided [113, 140]. As a result, it has been shown that clinical specimens are where most resistance mutations are localized, and some of them seem to impart no fee or extremely low prices. As an issue, fluoroquinolones' primary pharmacologic objective, DNA gyrase, is susceptible to resistance mutations that are occasionally very cheap or even negligible. Rifampicin-resistant rpoB mutations can also exist in some cases without having a negative effect on the fitness of their bearers [137, 141]

The second option is that bacteria contain changes that diminish the relative fitness costs of resistance without appreciably lowering the level of resistance. These variations are known as fitness-compensatory mutations, as a result, resistant microbes in the community have stabilized [137, 142, 143]. Indemnification happens through a variety of processes. The overwhelming of compensating alterations increases fitness by recovering the affected resistance protein via intra- or intergenic mutation. A bypass method, for instance, can decrease the requirement for the impacted functioning of the resistance protein, and eventually, a malfunctioning enzyme can be compensated for by manufacturing more of the affected enzyme [113, 140]. It is possible to find a long list of second site mutations that partial correlation resistance mutations to offset the fitness cost of the initial resistance imparting mutation. Bacterial FusA mutations that cause fusidic acid resistance are usually seen in association with other compensatory changes. Similarly, rpsL resistance variations to streptomycin typically result in compensating alterations in plenty of other genes [142, 144]

Despite the dearth of medication selection pressure, limited costs and compensating modifications work to boost the persistence of resistance microbial communities.

According to findings from 2 research into streptomycin resistant rpsL mutant sand fusidic acid resistant fusA mutant, the goal magnitude for compensating mutations frequently exceeds than twenty times that of reverting [113, 144]

Genetic methods including conjugation, cassette-based recombination and transposition, which are becoming more understood, are used to create these transportable components [145, 146]; despite probable fitness costs for some of the genes involved, the selective pressures that keep these resistant components together are less obvious. In *S. pneumoniae*, conjugative transposon Tn1545 contains genes for antibiotic resistance like macrolide-lincosamide-streptogramin B-type antibiotics, kanamycins, and tetracyclines, and is able to transfer to a newly isolated bacterial host cell by conjugation or transposition towards another genomic area [147].

In Enterobacteriaceae, integrons encode genes for drug resistance that aren't correlated to each other, like β-lactams, aminoglycosides, sulfonamides, and chloramphenicol [82]. Antibiotic resistance genes for numerous drug classes, including sulfamethoxazole, tetracycline, β-lactams, aminoglycosides, and chloramphenicol have been found on plasmids without integrons in Enterobacteriaceae [148-150].

E. Clinical Impact of Multi-Drug Resistance

People can be affected in an assortment of ways by antibiotics and bacteria that are resistant to them. The bacteria may horizontally transfer resistance genes towards other bacteria in the human gastrointestinal system if it occurred as a result of contaminated items [107, 151, 152]; Antibiotic remnant present in such sources may encourage the growth of bacteria that are resistant to antibiotics after consumption of food or water [153]. Resistant bacteria may enter the environment via feces from the guts of humans and animals.

As a result, it's possible that there's a linkage between *E. coli* in the ground, topography, and waterways encountered in the natural ecosystem and human and creatures. Considering that most graze cattle in green fields and imbibe from unprotected resources of water, it's conceivable that this is one of the factors contributing to the *E. coli* in dung Cow-borne that has sophisticated resistance. It's also probable that this approach contributed to the greater incidence of resistance seen in home drinkable water [153].

Vatopoulos and **Kalapothaki** [154] reported that, from the outpatients there were (52.6%) urine, (18.2%) respiratory, Pus (16.2%), and stool (0.7%). *E. coli*, *K. pneumoniae*, *Enterobacter* spp., *P. aeruginosa*, *A. baumanii*, and *S. aureus*. In terms of isolation rate, pathogenicity, and virulence, these species are the most important pathogenic obtained from inpatient or outpatient populations throughout most regions of the globe. Gram-negative non-fermenters are opportunist bacteria that are widespread in nature and cause infections in critically ill and immunocompromised humans.

Due to their propensity for surviving in a variety of habitats, particularly wet and damp conditions, many of these species have become troublesome on a global scale (e.g. *P. aeruginosa*), followed by *Acinetobacter spp.*, is the main source of infections and the agent responsible for gram-negative fermenter-related illnesses. Each of these infections has a different medication sensitivity [155].

El-Astal [156] reported that, out of 1278 urine samples, Positive monomicrobial cultures were found in 492 (38.5%) cases. Gram-negative bacteria accounted for 437 (91.0%) of the 480 positive bacterial cultures, whereas gram-positive bacteria accounted for 43 (9 percent). During the examination of UTI specimens, 12 yeast isolates (2.5% of 492) were discovered [157, 158]. Urinary tract infection (UTI) is one of the most prevalent bacterial infections to affect peoples throughout their life span. UTI is the second most common infectious presentation in community practice. Every year, nearly 150 million people worldwide are diagnosed with UTI, costing the global economy more than 6 billion [156]. **Wilson and Gaido** [159], reported that, many authors are concerned with UTIs being among the most prevalent bacterial illnesses, accounting for a large portion of the clinical microbiology laboratory workload. In acute infections of upper UTI in females resulting from encounter of a parasite and a host, this renal infection is due to uropathogenic strains of bacteria, *E. coli* is the predominant community-acquired bacterium in cases. The entrance of the urethral becomes infected whenever germs, often bacteria from the gastrointestinal tract, adhere to it and start to grow. *E. coli*, a species of bacterium that often dwells in the bowel, is the source of the majority of illnesses [156, 160]

Most pathogens responsible for UTIs are *Enterobacteriaceae*, with a high predominance of *E. coli*. This is especially true of spontaneous UTIs in females (cystitis and pyelonephritis). Other strains are less common, including *P. mirabilis* and more rarely gram-positive bacteria. Gram-positive pathogens are responsible for 5% to 15% of such infections [161].

El-Astal, [156] noted that, all over the world, *E. coli* accounts for 75% to 90% of UTI isolates, and *S. saprophyticus* accounts for 5% to 15% of cases of uncomplicated cystitis. A summary of the different microorganisms isolated during his study period, *E. coli* was the predominant uropathogen (52.5%) causing UTI, followed by *P. mirabilis* (9.8%) and *K. pneumonia* (9.2%). *E. faecalis* was the most common uropathogen (5.2%) isolated among the gram-positive bacteria.

Mazzulli., & Nicolle *et al.* reported that, most of pathogens isolated from community acquired uncomplicated urinary tract infections are consistent with *E. coli* isolated from episodes of *Klebsiella* species. *Proteus* spp., *Enterobacter* spp., *Citrobacter* spp., and then *P. aeruginosa* [161, 162].

Kochhar *et al.,* **and Nagamani** *et al.* reported that, most of the UTIs are caused by gram-negative organisms, though occasionally gram-positive organisms and fungi can

infect the urinary tract under certain circumstances, as the causative pathogens of UTI are most exclusively bacteria and yeast [158, 163]. In acute UTI, *E. coli* is the predominant organism causing infection across all age groups. Other aerobic gram-negative rods such as *Klebsiella* spp., *Proteus* spp., *Citrobacter* spp., *Acinetobacter* spp., *Morganella* spp., and *P. aeruginosa* are also frequently isolated, Invasive candidiasis may start in the urinary tract or secondary infection may it with gram-positive bacteria such as enterococcus and yeast. Candida infection of the kidneys is commonly connected with the use of a urinary catheter or broad-spectrum antibacterial drugs. The global expansion of *E. coli, K. pneumoniae, Haemophilus*, and numerous other ß-lactamase producers has become a serious therapeutic issue. Multi-drug resistant *E. coli* and *K. pneumoniae* strains are common in hospitals and are progressively isolated from community-acquired illnesses [164, 165].

MRSA is a prominent bacterium that poses a significant risk to human health and is a major burden on healthcare systems. According to one estimate, MRSA infections cost the healthcare system in the USA about 3 to 4 billion USD per year and cause ~19,000 deaths per year [166]. Among Gram-negative bacteria, increased antibiotic resistance in *A. baumannii* and *P. aeruginosa* has been reported worldwide, causing great concern in many countries. In multiple hospitals around the world, *A. baumannii* has been identified as the major cause of nosocomial pneumonia and bacteremia [167]. *P. aeruginosa* is also responsible for severe infections, such as pneumonia, often resulting in high mortality rates because of the lack of adequate therapeutic options and the development of resistance [168]. The increased level of antimicrobial resistance was not only recorded in the pathogenic bacteria but also in commensal bacteria (e.g., *E. coli*). This may be attributed to the misuse and overuse of antibiotics, which led to an increase in the level of resistance to such agents [151].

F. Environmental Contamination with Antibiotic Resistant Bacteria (ARB)

Several studies have reported the presence of ARB outside the hospital setting worldwide, in food, sewage, water, soil, air, animal, healthy human feces, restaurant flies and seagulls [169].

Although ARB has been detected for a long time, the massive use of antibiotics during the last decades in human and animal therapy for prophylaxis, as growth promoters in animal production or in agriculture, led to the selection of a high number of multidrug resistant microorganisms in different ecological niches. These microorganisms can be easily transmitted to humans by different routes [170]. These ARB can be transmitted to humans directly through the food chain and by direct contact with live and dead animals (veterinarians, farmers, and food manipulators) or indirectly through soil and contaminated waters [171-206]. MAR *Salmonella spp.* identified human infections that were discovered to have originated in an animal production context. Non-pathogenic bacteria (such as *Enterococcus spp.* and *E. coli*) can store and share antibiotic resistant genetic elements in intensive animal husbandry. As a result, they're

thought to be clear indicators of local antibiotic resistance [178, 185]

Not only have commensal and pathogenic multidrug resistant bacteria been recovered from swine, chickens, rabbits, fisheries, and other industrial production animals, but also from animals in the wild that came into contact with polluted sites [199, 204]. Even in the surrounding air of pig farms, *Enterococcus* spp. and *Staphylococcus* spp. carrying genes that confer resistance to tetracycline's, macrolides, lincosamide, and streptogramins were observed [172], suggesting that air might also act as a dissemination vehicle of these bacteria over long distances. The aquatic environment can be a reservoir of ARB and genes that can reach different mammals, including humans. Sewage, with its bacterial diversity, nutrients, and different molecules as antibiotics, is considered an excellent place for the development of multi-resistant strains called super-bugs [207].

Their misuse of humans and animals, on the other hand, has caused the rise of drug-resistant microorganisms [208]. Those bacteria are more difficult to combat, and the diseases they cause are now more refractory to treatment and costlier. As a result, significant impairment and even death may result [208, 209]. According to the World Health Organization [208], antibiotic resistance has drastically increased to high levels all over the world.

G. Biofilm Formation and its Role in Antibiotic Resistance

Microorganisms frequently confront challenging settings in the ecosystem [210]. It will be possible for them to survive if they can swiftly adjust to these modifications in their surroundings. Bacterial thrive strategies are activated by their ability to form communities known as biofilms [211]. These methods allow bacteria to cling to surfaces by secreting exopolymeric substances (EPS) [212], resulting in a three-dimensional enclosed matrix [213]. which is mostly made of polysaccharides, proteins, and DNA [214, 215]. A defensive mechanism against chemicals poisons and predators, such as biocontrol agents and antibiotics, is provided by the production of biofilm in bacteria [216]. Bacteria in biofilms are more robust than bacteria in planktonic or sessile states. Biofilm cells can endure up to 1000 times more antibiotic doses than planktonic counterparts and can even endure in environments contaminated with biocides and UV radiation [217].

Biofilm formation improves microorganisms' ability to resist harmful forces and colonies the environment. Biofilms are sessile bacterial populations that are linked to a substrate and embedded in an extracellular polymeric matrix created by the bacteria themselves. In comparison to planktonic cells, cells in this polymeric matrix have unique phenotypic, metabolic, physiological, and gene expression [218].

Due to the innate antimicrobial resistance provided by its own lifestyles, infectious microbiological biofilm is regarded as a global issue [219]. Microbial creatures were accountable for violent and severe cases of infection when they lived in a community in a clinical setting. This way of

combating this cellular architecture typically necessitates strong antibiotic doses for an extended period of time, and these techniques frequently fail, resulting in infection perpetuation [219]. Biofilms can lead to infections when they grow in medical equipment, in addition to their therapeutic constraints. Biofilms have prompted researchers all over the world to suggest or create biofilm control solutions [219]. Although progress is being made in biofilm studies, the management of biofilm - associated infections with antibiotic is still a mystery. Past pharmacokinetic (PK) and pharmacodynamics (PD) profiling of an antimicrobial drug can create an effective dosing schedule and prevent antimicrobial adaptation and resistant in biofilm-associated infections [220]. As a result of the difficulty in treating diseases linked to biofilms, including persistent infections and infections brought on by medical devices, there must be issues within healthcare that call for innovative ideas [221].

Chronic infections caused by bacterial biofilms include indwelling device infections, chronic wound infectious diseases, chronic urinary tract infections (UTI), cystic fibrosis pneumonitis, chronic otitis media (OM), chronic rhino sinusitis, gum disease, and recurrent tonsillitis [222]. Biofilm infections are one of the most serious problems in hospitalized and immunocompromised patients around the world, owing to their difficult and ineffective treatment with antibiotics. In biofilm, bacteria are not disrupted completely by antibiotics even high doses of antibiotics used *in vivo* [223-225]. The patient may be more at risk for death if the device is contaminated. Trauma-related infections brought on by orthopedic procedures and implantable devices that are challenging to cure with medications [226] to get rid of biofilm as well as cured infections brought on by biofilm, remove the implantation from the body [227] This might lead to a diseased limb losing its functioning ability [228, 229].

A slimy glycocalyx serves as the biofilm's anchorage for either biota or a biota superficies where a population of a sessile bacteria is implanted. Biofilm generating microbes generate an exogenous polymeric material, which is composed of extracellular DNA (eDNA), staphylococcal proteins, teichoic acids, and polysaccharide matrix [11, 210]. Polysaccharide intracellular adhesion (PIA) is a specific polysaccharide in glycocalyx composed of β-1,6–linked N-acetyl glucosamine residues (80–85%) and non-N-acetylated D- glucosaminyl residues that are an anionic fraction and contain phosphate and ester-linked succinate (15–20%) [11]. Surface proteins constitute a further alternate pathway to PIA for the development of biofilms in *S. aureus and S. epidermidis*. The extra - cellular matrix has extensive water-filled canals and an accumulation of β-lactamase, an enzyme that breaks down antibiotics [230], Because of the fact that it is a component of eDNA, and participates in the adaptable resistance mechanisms [231].

The production of bacterial biofilms is a complicated, multifaceted process. The stages of the biofilm development cycle are adhesive, attachable, aggregation, maturity, accumulative, and disassociation. The matured bacteria that are entrenched in the biofilm must be released from it as the final phase [58]

Antibiotics are less likely to harm bacteria trapped in biofilms than they are to harm planktonic bacteria. Because biofilm is hard to get rid of, there are significant clinical issues [226]. Antibiotic resistance, caused by biofilm and allowing microorganisms to flourish, is a physiological state whereby a gene modification is not brought about [232]. Efflux pumps, enzymes that break down antibiotics, and the charge of polymers all cause peptidoglycan to be impermeable [232], as well as specific gene product generated by biofilm communities [225] instead of the biofilm, are there additional bacterial strategies for antibiotic resistance? [225].

Beta-lactamases, efflux pumps, and specific gene products whose expression is altered by quorum sensing as a stress response are examples of antibiotic-degrading catalysts that might help biofilm develop more antibiotic resistance [225, 233]. Beta-lactamases are the mechanism through which biofilms tolerate beta-lactam drugs. A major contributor to the biofilm which results in resistance to beta-lactam medicines is the production of β –lactamases by microbes [225].

Resistance of biofilms such as oxygen restriction, poor metabolic activity and decreased antibiotic penetration into the biofilm are a major factor in biofilm tolerances to antibiotics, as well as genetic adaptation, like enhanced DNA repairing system gene alterations [225]. However, certain antibiotics, like colistin, only work against sluggish organisms found in the biofilm's deeper layers and not against speedily cells that have induced the LPS-modification (arn) operon to produce adaptive resistance [234]. The population of Persister cells in the biofilms of *S. epidermidis* can tolerate antibiotic inhibitory concentrations [234].

The rigorous respond comes into play during periods of famine and leads to antibiotic resistance, particularly fluoroquinolone resistance in *E. coli* biofilms [235]. Furthermore, multiple investigations have shown that *P. aeruginosa* efflux pumps are triggered more frequently in low oxygen circumstances [236].

Antibiotic entrance into biofilm is usually restricted when they interact with the structural elements of the biofilm matrix [225] Antibiotics are not diffused into the biofilm matrix as quickly as before [222].

Biofilm-embedded bacteria antimicrobial drug hypersensitivity decreases with planktonic form. The viciousness of agr mutant strains is lower than the wild type. Drug resistance of staphylococcal biofilm is affected by agr expression that enforces a fitness cost on S. aureus. Sub-lethal dosages of rifampin, ciprofloxacin and mupirocin have been shown to stimulate RNAIII synthesis which contributes the viability costs of bacterium in agr-positive microbial species [237].

The agr locus is involved in the adaptation of S. aureus to antibiotics. S. aureus develops resistance to antibiotics via modifying the agr locus. Against agr-defective bacteria, mupirocin, ciprofloxacin, and rifampin are more effective. When constructing antimicrobial chemotherapy, these antibiotics must only be employed in agr-deficient mutants or agr-negative *S. aureus*. In hospital-acquired *S. aureus*, agr-defective strains are often identified as infections caused by *Staph aureus* (HA-*Staph aureus*). The incidence of agr-defective strains among hospital-acquired *S. aureus* infections is substantial, ranging between 15% and 60%, due to widespread antibiotic use in hospitals [238].

Antibiotic drug susceptibility has been linked to Agr expression in biofilm producer *Staphylococcus aureus*. It was also discovered that rifampin doubled the action of oxacillin against agr mutant *S. aureus*, while oxacillin had no effect [237]. When vancomycin is present, an antibiotic, agr negative or agr malfunctioning isolates perform better than agr positive strains in regard to fitness. The thicker cell wall, which is the result of a combination of cell wall biosynthesis stimulation and decreased autolytic action, reduces vancomycin susceptibility in *VISA* (vancomycin-intermediate *S. aureus*) stimuli of the biosynthetic pathways and a reduction in autolysis. Agr mutations and the development of *VISA* have just been linked. Vancomycin sensitivity of *VISA* is diminished by agr faults that diminish autolysis [239].

Melittin's unique mechanism, like that of other antimicrobial peptides, is based on the phospholipid bilayer structure of the targeting bacterium and also evades conventional antimicrobial therapies that could influence peptide binding positions in the cellular membranes [240-242].

Antibacterial peptides seem to be well for their excellent antimicrobial action against microbial membranes and limited development of antimicrobial resistance [243-245]. The existence of latent bacteria populations (sleepers) within biofilms is one of the main motives that biofilm structuring could enable high antibiotic resistance. Classical antibiotics, which typically rely on actively growing cells, have a hard time killing these biofilms [246]. Certain antimicrobial peptides, such as melittin from (BV), could solve this problem by permeabilizing microbial membranes, causing membrane disintegration and cellular damage, even in inactive cells at the biofilm's Centre [245, 247].

H. Finding Strategies Against Antibiotic Resistance

Finding solutions to combat the spread of antibiotic resistance is a serious global concern for the bioscience community and public health. Human-pathogenic bacteria that are resistant to one or more antibiotics have increased dramatically globally over the last few decades [248]. More illnesses caused by resistant germs are resistant to standard treatment, and even last-resort medications are losing their effectiveness. In addition, over the last few decades, the pharmaceutical industry's pipeline for developing new antibiotics has dried up.

The World Health Organization's recent World Health Day, with the concept "Combat drug resistance: no action today means no cure tomorrow," sparked a boost in research activity, and several hopeful techniques have been created to

reintroduce treatment options for infectious agents caused by resistant bacterial strains [248].

Thus, in light of the evidence of the rapid global spread of resistant clinical isolates, it is critical to discover new antibacterial agents. However, given the history of the rapid and widespread establishment of tolerance to recently launched antimicrobial drugs, even new antibiotic families are likely to have a limited lifespan [249]. Due to this, scientists are more focusing on herbal remedies in an effort to find fresh inspiration for creating more effective medications to combat MDR microbiological populations [250].

➢ *Plants as a Source of Antimicrobials*

The necessity to create innovative and more potent microbiological medications is highlighted by the rise of microbial resistant to the primary antibiotic being used [251, 252].

Medicinal plants are viewed as a viable source for the discovery of novel molecules since they have a greater molecular variety than chemically synthesized products [253, 254]. Plants create bioactive substances in response to being penetrated by bacterium, fungus, worms, viruses, and perhaps other agents [254]. Plants produce a variety of chemical compounds with antimicrobial characteristics, and scientific research into their medicinal potential is important for antibiotic activities against human infections [255, 256].

Insecticidal, bactericidal, anti - viral and fungicidal properties have indeed been found to be present in a wide variety of bioactive ingredients found in plants [257]. The antibacterial properties of plant extracts, essential oils, and other plant extracts have sparked an interest in using crude extracts or bioactive components to limit bacterial growth [257, 258]. Natural substances that are beneficial to human wellness may be found in large quantities in plants. Anti-oxidative and anti-microbial chemicals can be obtained from medicinal plants. Many research have looked into the antimicrobial characteristics of plants, and many of them have been exploited as therapeutic options due to their antibacterial capabilities [259]. Medicinal plants contain significant levels of bactericidal and anti - oxidative ingredients [260].

Plants also produce a range of antimicrobial peptides, which can be classified into several categories: thionins, defensins, lipid transfer proteins, cyclotides, and snakins, to name a few [117].

Natural items have been utilized in traditional medicine across the world for thousands of years, long before antibiotics and other modern medications were introduced.

The antibacterial potency of several plants in disease treatment has been astounding. Local groups are thought to have employed roughly 10% of all flowering plants on the planet to cure different illnesses, while only 1% have been recognized by modern scientists [261]. Plants having antimicrobial compounds are frequently sought after due to

their widespread usage as treatments for a variety of infectious disorders [262].

Plants encompass a wide variety of secondary metabolites, including tannin, alkaloid, and flavonoid, all of which have antibacterial property in vitro [263]. Because of its accessibility, minimal side effects, and lower toxicity, a majority of phytotherapy books have recommended multiple therapeutic plants for treating infectious disorders [215]. Several studies on the antibacterial activity of various medicinal herbs have been conducted [264, 265]. UTIs, gastrointestinal illnesses, respiratory ailments, and dermatitis have all been treated using plants [266, 267]. Medicinal plants are the best method for getting a wide range of medications, according to the WHO [268].

Nine plant-based spices (sea fennel, savoury, cumin, basil, pickling herb, laurels, mint, myrtle, and oregano) had their antibacterial properties evaluated at three different concentrations (1, 10, and 15%) and on a variety of microorganisms (*E. faecalis, A. niger, B. cereus, R. oryzae, E. coli, S. cerevisiae, S. aureus, C. rugosa, S. typhi and Y. enterocolitica,*). According to its findings, the inhibitory effect of the extracts examined differed between **Özcan** and **Erkmen** [269]. To ascertain the antibacterial properties of its extraction yields, 2 specimens of thyme were picked in Iran and one from Oman, while two samples of clove were taken in Sri Lanka and Zanzibar **Nzeako** *et al.* [270].

Al-Muhna [271] Studied the antibacterial activity of the *T. vulgaris* and *E. camaldulensis* the antibacterial activity against *L. monocytogenes* was examined. The agar well diffusion method was used to assess the inhibitory activity. The extracts of two examined plants indicated antimicrobial activity against the tested species. However, the efficiency of the extracts was greatly impacted by the solvent used in the extraction, as well as plant species and concentration. The water extract seemed to be the most efficient against the pathogen investigated. Their results showed that the aqueous extract of *T. vulgaris* was the most active agent against the test organism, while the aqueous extract of *E. camaldulensis* appeared to be the second-most effective agent.

Witkowska *et al.* [272] assessed and compared the antimicrobial effects of extracts from (30) various commercial spices and herbs routinely used in the preparation of ready meals. Using the micro dilution broth methodology, several spice extracts were tested for antibacterial activity against *L. innocua*, bacteria *of E. coli, S. aureus, and P. fluorescens*. Extracts of celery, oregano, clove, rosemary, and saga in ethanol and hexane had highly antibacterial activity against all tested pathogens. Water extracts, on the other hand, had little or no antibacterial action. Flow cytometry showed that spices and herbal bioactive compounds disrupted cellular membranes, whereas measurement of bacteria's intra and extracellular ATP content suggested that a rise in extracellular ATP seemed to be partially attributable to intracellular leaking.

The checkerboard approach did not reveal any synergistic effects, but when oregano was coupled with sage or rosemary versus L. innocua or S. aureus, some additive effects were detected. Their study has demonstrated that some commercial spice extracts have antimicrobial activity against tested bacterial species.

Santoyo *et al.* [273] observed that camphor and verbenone showed activity against *S. aureus* and *E. coli*. [274]. Cadinene has been shown to be active against a variety of pathogens, particularly *Pseudo. aeruginosa and K. pneumoniae* [274]. Those results emphasize why extracts are effective against Gram-negative microbes. Many investigations have shown that plants often used in traditional medicine have antibacterial activity [275, 276]**.**

Ríos and Recio [277] highlighted that the presence of activity is highly interesting in the event of extract concentrations less than 0.1 mg/mL. Previously employed individuals.

Previous workers **Nair** and **Chanda** [278]. Said that antimicrobial effects are thought to be caused by the suppression of numerous cell mechanisms, the process culminates in ions leaking through cells, that occurs following a rise in permeable of cell membrane [279]. Because of their essential oils, saponic, flavonoids, tannic and phenols, botanicals are regarded to have antimicrobial capabilities [280].

In a study conducted by **Kowero** *et al.* [281], *P. barbatus* had a significantly broad MIC range extending from 3.12 to 12.5 mg/mL. The MIC values for *P. barbatus* extracts against *S. typhi* and *K. oxytoca* were 3.12 mg/mL. Furthermore, *P. barbatus* had a MIC value of 3.12 mg/mL against *P. aeruginosa* [282].

Araújo *et al.* [283] noticed that streptomycin and ethanol extraction worked together synergistically. In vitro tests versus P. aeruginosa ATCC 27853 and E. coli ATCC 43895 revealed synergic action of *P. barbatus* extract with streptomycin. *R. officinalis* extracts plus streptomycin had a synergistic impact on *E. coli* ATCC.43895.

Felipe *et al.* [284] found that, by using the broth micro dilution method, the antimicrobial properties of Lamiaceae

plant extracts were tested versus clinical strains of multi-resistant Gram-negative bacteria. All extracts were active against at least two bacterial species with MICs ranging from 0.5 to 2.0 mg/mL, which were promising results.

S. aureus, Bacillus subtilis, Escherichia coli, Proteus vulgaris, Pseudomonas aeruginosa, Salmonella para typhi B, and *Klebsiella pneumoniae* have all been proven to be susceptible to the aqueous extract of *Z. spina-christi* stem [187].

In comparison to eight drugs, *Z. spina-christi* stem bark aqueous extract showed highly substantial antibacterial effect activity against Brucella abortus, Brucella melitensis, Proteus spp., Klebsiella spp., P. aeruginosa, E. coli, and Enterobacter spp. [188]**.**

S. aureus isolated from eye infections was found to have good antibacterial action in an alcoholic extract of the leaves. For 1 mg/ml of the extract, a 20 mm inhibitory zone was observed [189].

Salmonella typhi, Proteus mirabilis, Shigella dysenteriae, E. coli, K. pneumonia, B. melitensis, Bordetella bronchiseptica, and *Pseudo aeruginosa* were also active against the leaves. By using a concentration of 100 mg/ml, the maximum activity (20 mm) was achieved against B. bronchisept [190].

In vivo, *E. coli, P. aeruginosa, and Candida* albicans were all inhibited by *Z. spina-christi* pulp aqueous extract. *E. coli and Candida albicans* have MICs of 6.25 mg/ml for the extract. For Streptococcus pyogenes, the pulp aqueous extract had a minimum bactericidal concentration of 12.5mg/ml [178].

➤ *Animal-Derived Antimicrobials (Chitosan)*

Chitosan is a cationic polysaccharide composed of β-1, 4 linked D-glucosamine and N Acetyl-D- glucosamine residues [285]. It's only found in a few fungi naturally (Mucoraceae). After cellulose, chitin, on the other hand, is the most prevalent polymer in nature [20]. Crustacean shells, insect cuticles, and fungal cell walls are the most common places where it can be found [286]. Figure (1) shows the structure of chitin and chitosan.
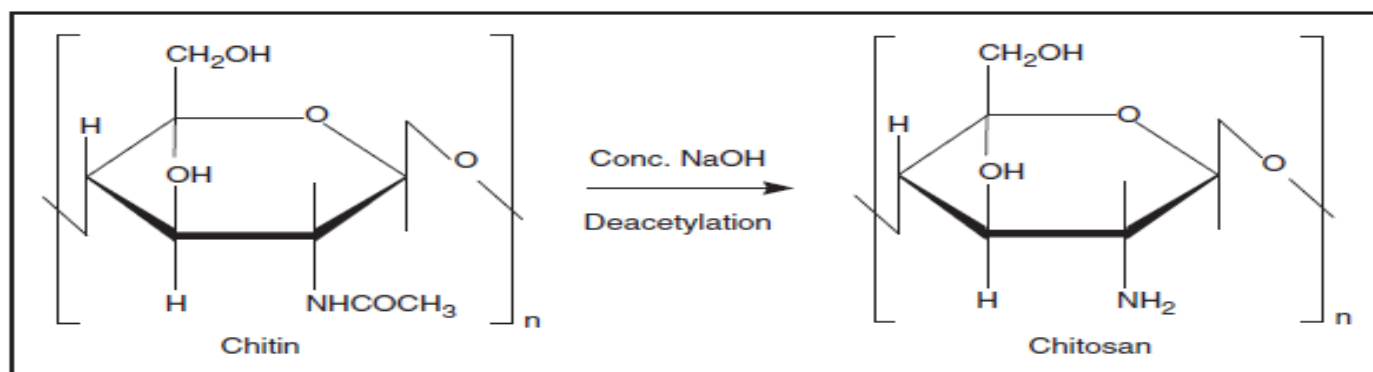

Fig 3: Structure of Chitin and Chitosan. Adapted from Dutta et al. (2011).

Sea creatures (shrimps) and arthropods' exoskeletons include chitosan, a naturally occurring polycationic biodegradable polymer [287]. There are low-molecular-weight derivatives of chitosan that have been partly and completely deacetylated and have potent antimicrobial and anti-fungus properties (**Kong et al., 2010).**

Chitosan is considered a safe food additive. However, *L. monocytogenes, S. aureus, B. cereus, S. dysenteriae, E. coli,* and *Salmonella Typhimurium* as examples of Gram positive and negative pathogens have been shown to be resistant to chitosan derivatives (**Gyawali** and **Ibrahim, 2014**). Chitosan is spark considerable interest in the creation of recyclable edible films, either alone or in combination with other antibacterial compounds (**Elsabee** and **Abdou, 2013**).

- *Properties of Chitosan*
  The biomedical characteristics of chitosan have included antibacterial properties, anti-cholesterol proprietaries, anti - oxidative, anti-inflammation, anti-cancer effect, analgesic and hemostats actions, bio-adhesive ability, angiogenic stimuli, phagocytic, granulation and scar formation, and adsorption enhancer. Chitosan has also been demonstrated to be safe, degradable, and excellent biocompatibility (permeation enhancer) [20].

- *Mechanisms of Antimicrobials Action of Chitosan*
  Chitosan's antibacterial activities have been extensively researched and validated (**Kong et al., 2008; Dutta et al., 2009**). However, many explanations for chitosan's antibacterial actions have been postulated. The initial suggested antibacterial mechanism of chitosan occurs as a result of electrostatic interactions between the chitosan amine group and the negative charge components of the outer cell (lipopolysaccharides and proteins), producing cellular membrane deformation and intracellular leaking [288, 289]**.**

A study by **Liu et al.** [290] *Staph. aureus and E. coli* were treated with 0.5 and 0.25 percent 78 kDa chitosan showed a 1 log decrease after 5 minutes, full inactivation of *E. coli* after 120 min, S. aureus remained unchanged after 120 minutes. A transmission electron microscope was used to investigate the cells. when it was found that E. coli possessed a chitosan-coated outer membrane that was destroyed while the inner membrane was undamaged. *Staph. aureus* displayed intracellular material leaks and newly generated cells formed lacking membranes or cell walls on the exterior Another research by **Helander et al.** [291], 0.025% of 85% DDA chitosan was applied to *E. coli and S. Typhimurium*, altering the exterior the cell's membrane and forming a layer surrounding *E. coli.*

It has been hypothesized that while chitosan inhibits cellular physiological processes, it has differing effects on Gram positive and cells that are Gram-negative [292]. He theorized that in Gram positive organisms, higher molecular weight chitosan forms a polymer membrane that prevents nutrients from entering and exiting the cell, whereas in Gram negative organisms, lower molecular weight chitosan enters the cell and binds to electronegative substances, causing

flocculation in the cytoplasm and disrupting physiological functions [292].

The third hypothesized mode of action involves infiltrating the cell of the bacterium and interacting with DNA to suppress mRNA and protein synthesis [293]. Another antibacterial mechanism proposed for chitosan is the chelation of critical minerals for development [289].

Kong et al. [288] discovered that 1456 kDa chitosan microspheres potentially destabilizing the *E. coli* cell by chelating Mg^{2+} from the outer membrane. However, depending on the kind of microbe and the properties of chitosan, the antimicrobial activity of chitosan may include all of the postulated methods of actions.

As well as, it was found that pre-harvest tests revealed that chitosan has indirectly antiviral effect through inducing tolerance inside the plant tissues [294]. By triggering the synthesis of abscisic acid and conferring plant resistance to the virus, 0.15% 76 kDa chitosan for tobacco necrosis virus resulted in a 95.2% decrease [295]. Chitosan's ability to disrupt the virus' structure integrity represents the first post-harvest method which has been suggested [296].

Kochkina and **Chirkov** [296], Using the technique of electron microscopy, it was possible to observe how chitosan reduced the number of viruses tails fibers with receptors and caused the virus coat to compress, revealing the DNA of phage T2 and 1-97A.Chitosan may bind with the virus capsids' negatively charged, according to a different theory [169]. They found that 0.7% 53 kDa chitosan caused a 1.7 log reduction in MS2, which could be connected to the negative charges MS2's 3.9 isoelectric point [170].

The third suggested tactic appears to be preventing phage infections. According to a study, chitosan may stick to the viral particles in the cell to stop infectious bacteriophages such bacteriophage T2 and T7 from lysing after adhering to hosts [296]. A phase in the replicate cycle is impeded by yet another chitosan strategy that has been suggested [22].

Bacteriophage 1-97A replication in *B. thuringiensis* was successfully inhibited by chitosan, according to the study's authors, who theorized was because the phages' internal reproduction was stopped. To fully comprehend the efficiency and processes of chitosan's impact on foodborne viruses, additional research must be done in this area. For the chitosan's antifungal action, similar processes have been postulated [296].

The cell's plasma membrane comes into touch with the chitosan in the first step, which causes intracellular substances to flow out [297].

Badaway et al. reported that chitosan and chitosan derivative products of lower than 120 kDa (85% DDA) were employed at 1% doses to discover that Chitosan caused a permeability shift in the plasma membrane, which inhibited *B. cinerea* growth**. Seyfarth et al.** found that when *C. albicans, C. krusei,* and *C. glabrata* were exposed to 120 kDa

chitosan hydrochloride, the plasma membrane was disrupted, resulting in permeable cells [298].

Saccharomyces cerevisiae cell walls were discovered to be structurally damaged by 0.1% chitosan, which resulted in growth inhibition and a 1 log decrease in the initial minutes of therapy. Chitosan has also been proven to be successful in reducing *B. cinerea* growth [299]. The buildup of chitosan in the cell wall as a growth inhibitor is a second hypothesized mechanism. **El Ghaouth *et al*.** found that the aggregation of chitosan in the cell wall of microorganisms produced amino acid leakage and also morphological abnormalities. Ca^{2+}, Zn^{2+}, and other crucial metals for development are chelated in the third hypothesized method [300-310].

III. CONCLUSION

The review has underscored the grave threat posed by the rise of multidrug-resistant bacteria to global health, highlighting the inadequacy of current antibiotic therapies in the face of evolving bacterial defenses, particularly in the context of biofilm formation and the spread of resistance genes. The critical analysis of biofilms elucidates their role not only as a physical barrier to antibiotic penetration but also as a breeding ground for resistance, complicating the treatment of infections and contributing to the persistence and spread of MDRB. The exploration of antimicrobial peptides, with a focus on melittin, presents a promising avenue for overcoming these challenges. Melittin's broad-spectrum activity, ability to disrupt biofilms, and potential to evade traditional resistance mechanisms position it as a valuable candidate in the development of novel therapeutic strategies against MDR pathogens.

Furthermore, the review highlights the necessity for a multifaceted approach to combat antibiotic resistance, incorporating the development of new antimicrobials, such as AMPs, alongside strategies to prevent the formation and spread of biofilms. It calls for increased research into the mechanisms of biofilm resistance and the exploration of natural compounds with antimicrobial and anti-biofilm activities. The urgency for innovation in antimicrobial strategies is clear, as is the need for global collaboration in research, policy-making, and public health initiatives to address the escalating threat of antibiotic resistance.

In conclusion, while the challenges posed by MDRB and biofilms are formidable, the potential of antimicrobial peptides like melittin offers a beacon of hope. By continuing to explore and understand the complex interactions between bacteria, biofilms, and antimicrobials, we can pave the way for the development of effective treatments that can outpace bacterial resistance, safeguarding the efficacy of antibiotics for future generations.

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