Volume 1, Issue 2, July-September 2026

INTERNATIONAL JOURNAL OF Medical and Healthcare Sciences (IJMedHS)

e-ISSN: AWAITING

OPEN ACCESS

Journal homepage: https://jmedhsscience.com/

Non-Antibiotic Anti-Virulence Strategies Against Multidrug-Resistant Bacterial Pathogens: A Review

Sneha D. Patil[1], Anuja D. Nirwane[2*], Ankita V. Chavan[3], Anuja C. Khatale[4], Nilesh B. Chougule[5]

[1,2,3,4,5]Department of Pharmacology, Ashokrao Mane Institute of Pharmacy Ambap, Wathar 416112, Maharashtra, India.

Corresponding Auther:- anujanirwane123@gmail.com

Article Info

Received: 28 July 2026
Accepted: 30 August 2026
Published: 07 September 2026

*Anuja D. Nirwane.,
Non-Antibiotic Anti-Virulence Strategies Against Multidrug-Resistant Bacterial Pathogens: A Review, *International Journal of Medical & Healthcare Sciences [IJMedHS], 1(2), 39-50*
DOI:

ABSTRACT

The increasing prevalence of bacteria resistant to multiple antimicrobial drugs has become a major global health concern, creating an urgent need for alternative approaches to infection management. This review was conducted to evaluate the potential of non-antibiotic agents as anti-virulence therapies that target bacterial pathogenic mechanisms without directly killing bacteria. Published studies on natural compounds, probiotics, bacteriophages, antimicrobial peptides, nanoparticles, and repurposed drugs were examined. The findings indicate that these agents can reduce bacterial pathogenicity by inhibiting adhesion, neutralizing toxins, disrupting cell-to-cell communication, preventing biofilm formation, and modulating host immune responses. Advances in screening technologies and computer-assisted drug design have further supported the identification of agents targeting specific virulence pathways. These approaches may reduce the development of antimicrobial resistance while preserving beneficial microorganisms. In conclusion, non-antibiotic anti-virulence therapies represent a promising strategy for controlling resistant bacterial infections and may improve future treatment outcomes when used alone or alongside conventional antimicrobial agents.

Keywords: Antibiotic agents, Antivirulence therapy, Antimicrobial resistance, Bacterial pathogenicity, Biofilm formation, Bacteriophages, Drug repurposing.

1. Introduction

Antimicrobial resistance has emerged as one of the most serious public health challenges worldwide. According to the World Health Organization, antimicrobial resistance is responsible for millions of infections annually and significantly increases morbidity, mortality, and healthcare costs. The rapid emergence of multidrug-resistant bacterial pathogens has reduced the effectiveness of conventional antibiotics and highlighted the urgent need for alternative therapeutic approaches.[1] The emergence and spread of multidrug-resistant (MDR) bacteria makes the new models for antibacterial drug discovery 61 especially clear. A 2017 World Health Organization report identifies ESKAPE pathogens—Enterococcus fecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, and species of Enterobacter—as priority pathogenic bacteria that exhibit lethal antibiotic resistance. [2] The advent and dissemination of MDR pathogens represent a global public health threat. Drug resistance is highly diverse and complicated.[3] The reasons are multifactorial such as over/ mis-use of antibiotics like unbridled prescriptions, using inept doses and schedules, incomplete or prolonged course of treatment; delay in diagnosis (lack of quick an easy laboratory support including point-of-care tests), insufficient level of infection prevention and control actions at health facilities coupled with weak adherence to hygiene measures, lack if sanitation (Chinemerem

Nwobodo et al., 2022) and the potential genetic flexibility of microorganisms.[4] In addition to this use of antibiotics are also used as a routine in the production of livestock and in farming and agriculture, which unavoidably contribute towards the drug-resistant strains that can move up through the food web or chain to humans. [5]

The increase in bacteria resistant to antibiotics is one of the largest threats to the healthcare sector today. A serious threat to human health, the number of deadly pathogenic multidrug-resistant bacteria (MDR) is growing every day. [6]

Conventional antibiotics and non-antibiotic drugs are thought to have different antivirulence characteristics.[7] These drugs target the "virulence factors" of bacteria, the mechanisms through which disease is brought on, rather than eradicating or preventing bacterial growth.[8] Toxins that harm human tissues, proteins that bacteria use to stick to cells, and systems for immune evasion or communication are a few examples of these virulence factors.[9]

Anti-virulence drugs prevent infections or lessen the damage that bacteria cause by blocking these virulence factors.[10]

Crucially, since these drugs do not eradicate bacteria, there is less pressure on them to become resistant. Consequently, bacteria that are resistant to several medications may be successfully.[11]

Anti-virulence drugs prevent infections or lessen the damage that bacteria cause by blocking these virulence factors. Crucially, since these drugs do not eradicate bacteria, there is less pressure on them to become resistant. As a result, bacteria that are resistant to several medications can be successfully treated without making their resistance wors. [12]-[15]

These medications may stop bacteria from adhering to cells or creating protective clusters known as biofilms. [16] Additionally, prevent the release of toxins by bacteria disrupt the communication between bacteria that regulates harmful behaviours. [17] By impairing the bacteria's defence, you can aid the immune system in eliminating infections. These side effects have been discovered in certain non-antibiotic medications that are already being used to treat other conditions, providing a promising short cut to novel therapies. [18] All things considered, anti- virulence medications offer a fresh approach to treating infections that may be used in addition to or instead of conventional antibiotics and aid in the better management of resistant bacteria. [19]

The objective of this review is to summarize current knowledge regarding non-antibiotic anti-virulence therapies, their mechanisms of action, clinical applications, advantages, limitations, and future prospects for combating multidrug-resistant bacterial infections. [20],[21]

Materials and Methods

A comprehensive literature search was conducted using PubMed, Scopus, Web of Science, ScienceDirect, and Google Scholar databases.[22] Articles published between 2015 and 2025 were screened using keywords including antimicrobial resistance, anti-virulence therapy, non-antibiotic agents, quorum sensing inhibition, biofilm disruption, bacteriophages, probiotics, nanoparticles, and drug repurposing.[23] Original research articles, review articles, and clinical studies published in English were included. Studies lacking sufficient scientific evidence or relevance to anti-virulence mechanisms were excluded.[24]

Classification of multidrug-resistant Bacteria: -

Table.1 :-Classification of multidrug-resistant Bacteria

Sr No	Type	Information	Reference
1	Based on Resistance Spectrum	Resistance to at least one agent across three or more antibiotic classes is referred to as multidrug-resistant, or MDR. Extensively drug-resistant, or XDR, bacteria exhibit resistance to all but one or two antibiotic classes. Resistance to every antibiotic on the market is known as PDR (Pandrug- resistant).	[25]
2	Based on Mechanism of Resistance	Enzymatic inactivation: E. Coli and Klebsiella pneumoniae produce enzymes called β-lactamases (ESBL) and carbapenemases that inactivate antibiotics. Efflux pumps: Pseudomonas aeruginosa and Staphylococcus aureus both exhibit efflux mechanisms, which pump antibiotics out of their bacterial cells. Target modification: As seen in MRSA (caused by the mecA gene) and VRE (caused by the van gene), antibiotic targets are changed. Decreased permeability: Alterations in porins, which are present in Enterobacter and Pseudomonas species, block drug entry.	[26]

3	Based on Gram Staining	1. Gram-positive MDR bacteria: Enterococcus species (VRE, or vancomycin-resistantEnterococcus), Streptococcus pneumoniae (MDR Streptococcus pneumoniae), and Staphylococcus aureus (MRSA, or methicillin-resistant Staphylococcus aureus) have all developed resistance. 2. Gram-negative MDR bacteria include E. coli and Klebsiella that produce extended-spectrum β-lactamase (ESBL), as well as Enterobacteriaceae that have developed carbapenem resistance (CRE). Multidrug resistance has also been observed in Pseudomonas aeruginosa and Acinetobacter baumannii.	[27]
4	Based on Clinical Relevance / WHO Priority	1. Multidrug-resistant Acinetobacter, multidrug-resistant Pseudomonas, and carbapenem-resistant Enterobacteriaceae (CRE) are examples of critical priority pathogens. 2. High priority: Enterobacteriaceae that produce extended-spectrum β-lactamase (ESBL) and Salmonella that are resistant to multiple drugs have been identified as high priority pathogens.	[28]

Bacterial virulence and resistance Mechanisms: -

To infect hosts and evade the immune system, bacteria employ a range of specialized molecules known as virulence factors. [25] Adhesions and pili are used to stick to cell surfaces, surface structures like capsules are made to provide defence against immune attack, toxins are made to damage or kill host cells, and enzymes are released to break down host tissues. Additionally, mechanisms like biofilm formation are used to protect bacteria from immunological reactions and antibiotics. [26]

Chromosomes, plasmids, or bacteriophage DNA contain genetic elements that encode virulence factors. Resistance and virulence traits are transferred between bacterial species through horizontal gene transfer, which causes new and more virulent pathogens to emerge quickly. [27] Many virulence factors, such as toxins and resistance genes, are acquired by pathogenic strains of Staphylococcus aureus and E. coli through bacteriophages and plasmids. [28]

A number of mechanisms contribute to antibiotic resistance. Antibiotics are pumped out of cells by efflux systems, biofilms are formed to block drug access, target sites are changed to prevent drug binding, and bacteria produce enzymes like β-lactamases to break down antibiotic molecules. [29]These tactics guarantee bacterial survival even when strong antibiotics are present, making multidrug-resistant infections a serious worldwide concern. [30,-[31]

Efflux Pump Mechanism: -

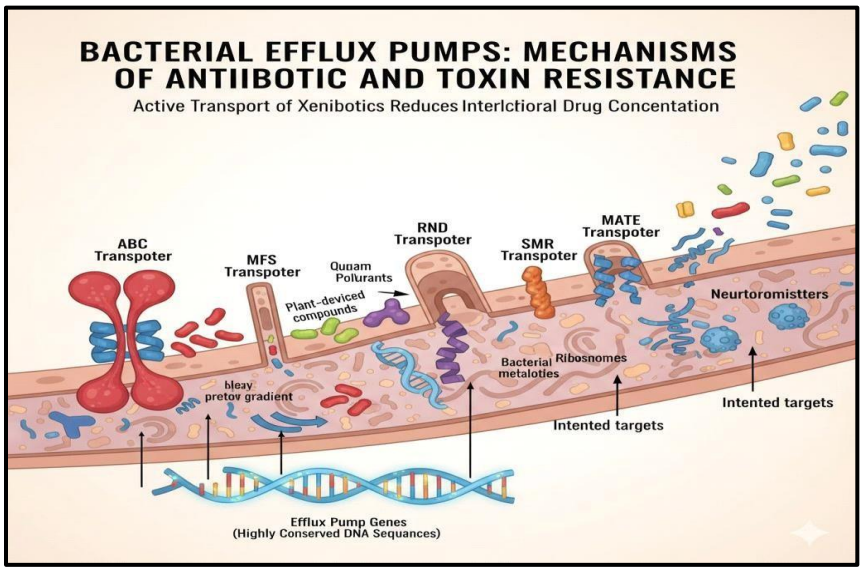

Fig 1:- Efflux Pump Mechanism
(Source: Created by the authors based on published literature).

Clinical significance:

Efflux pumps contribute significantly to multidrug resistance by decreasing intracellular antibiotic concentrations. Overexpression of efflux systems has been reported in Pseudomonas aeruginosa, Acinetobacter baumannii, and Staphylococcus aureus. [32] The ATP-Binding Cassette (ABC) transporters and the Major Facilitator Superfamily (MFS) are linked to antibiotic

resistance.[33] Efflux pumps transport antibiotics out of the bacterial cell, causing a low intracellular concentration that keeps the medications from getting to where they're supposed to. Heavy metals, organic contaminants, compounds derived from plants, quorum-sensing signals, bacterial metabolites, and neurotransmitters can all have an impact on the efflux process.[34] With very few exceptions, the genomes of almost all microorganisms contain highly conserved DNA sequences that encode efflux pumps. The process by which materials are actively moved out of microorganisms by efflux pumps is known as active efflux. It is considered a critical component of xenobiotic metabolism. Bacterial pathogens develop different kinds of resistance as a result of the adaptation of these efflux pumps, which divert toxins from the cytoplasm into the extracellular medium. [35]-[37]Antibiotics are prevented from reaching their molecular targets by this process, which maintains low intracellular drug concentrations. It has been discovered that bacteria possess several families of efflux pumps, each of which operates through somewhat different molecular pathways. These include the ATP-Binding Cassette (ABC) family, the Resistance-Nodulation-Division (RND) family, the Small Multidrug Resistance (SMR) family, and the Multidrug and Toxic Compound Extrusion (MATE) family. [38]-[40]

Enzymatic Inactivation Mechanism: -

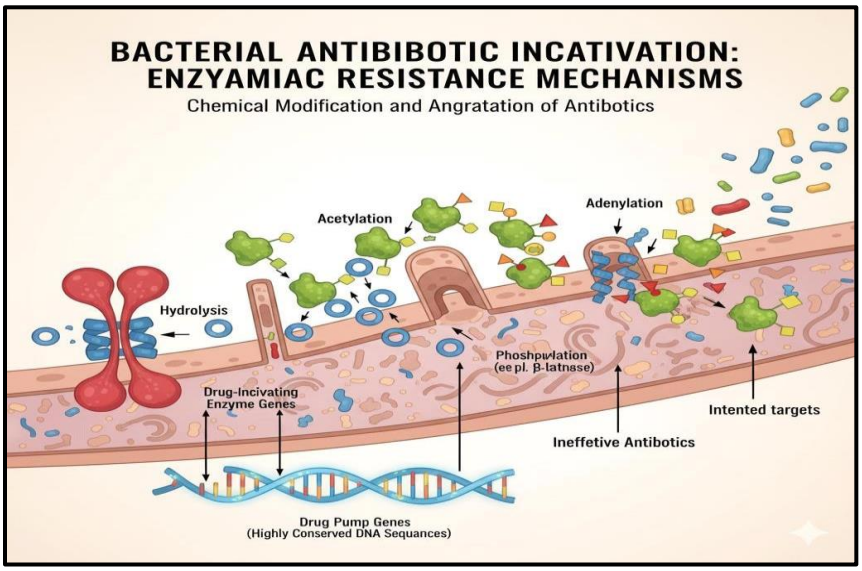

Fig .2: -Enzymatic Inactivation Mechanism
(Source: Created by the authors based on published literature).

Examples of clinically important β-lactamases include TEM, SHV, CTX-M, KPC, NDM, and OXA-type enzymes. These enzymes are responsible for resistance against cephalosporins and carbapenems in many Gram-negative pathogens. According to this mechanism, bacteria produce drug-inactivating enzymes (green in the image), which chemically alter or degrade antibiotic molecules (blue circles) and make them ineffective before they reach their target sites. These enzymes are commonly found in the periplasmic space, which is the region between Gram-negative bacteria's inner and outer membranes, or released into the extracellular environment. [41]-[43]

This mechanism frequently involves the following reactions:

When an antibiotic undergoes hydrolysis, its chemical bonds are broken (for example, β- lactamase hydrolyzes penicillin's β-lactam ring).

The antibiotic molecule is chemically altered by acetylation, phosphorylation, or adenylation, which stops it from attaching to its target (a process frequently seen in aminoglycosides) [44]

Biofilm Protection Mechanism: -

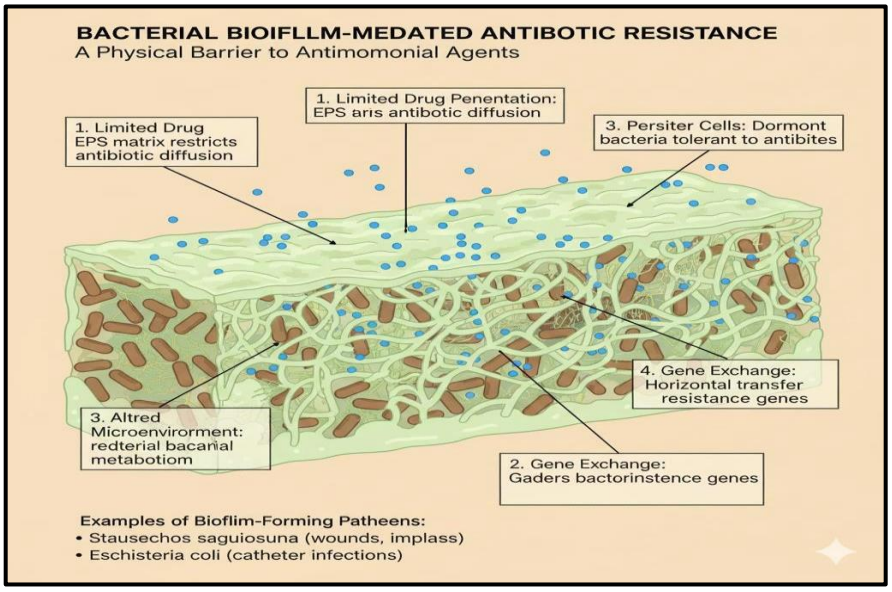

Fig no.3: - Biofilm Protection Mechanism
(Source: Created by the authors based on published literature).

Biofilms are organized bacterial communities that are covered in an extracellular polymeric substance (EPS) matrix, which appears light green in the image. This matrix is regarded as a physical and chemical barrier that limits the penetration and efficacy of antimicrobial agents (blue dots). Polysaccharides, proteins, lipids, and extracellular DNA (eDNA) make up the EPS matrix, by which a dense protective layer is formed around the bacterial community (brown rods). [45] Bacteria in biofilms demonstrate increased resistance to host immune responses and antibiotics for a number of reasons:

1. 1.Limited Drug Penetration: The EPS matrix limits the spread of antibiotics, which lowers their concentrations inside the biofilm.[46]
2. 2.Modified Microenvironment: The biofilm creates gradients of pH, oxygen, and nutrients that slow bacterial metabolism and reduce antibiotic susceptibility.[47]
3. 3.Persister Cells: During antibiotic exposure, a subset of metabolically dormant cells is preserved, enabling survival and subsequent repopulation.[47]
4. 4.Gene Exchange: The close proximity of bacterial cells promotes horizontal gene transfer,
5. cluding the transfer of resistance genes.[48]

Examples of Biofilm-Forming Pathogens:
Pseudomonas aeruginosa (in cystic fibrosis lung infections) Staphylococcus aureus (in chronic wound and implant infections) Escherichia coli and Klebsiella pneumoniae (in urinary catheter-associated infections)

(Table 2. Major Biofilm-Producing Bacterial Pathogens and Related Infections)

Pathogen	Biofilm-associated Infection
Staphylococcus aureus	**Implant infection**
Pseudomonas aeruginosa	**Cystic fibrosis**
Escherichia coli	**Catheter infection**
Klebsiella pneumoniae	**Urinary tract infection**

Key molecular mechanisms that enable bacterial virulence: -
Adhesion: Adhesins, pili, and fimbriae are the mechanisms by which bacteria adhere to the surfaces of their hosts. This phase is thought to be a crucial first step in infection and colonization.

Production of Toxins: Many bacteria secrete toxins, such as endotoxins and exotoxins, which harm host tissues, interfere with immune responses, or interfere with regular cellular functions. Cholera and diphtheria toxins are two examples.

Invasion and Evasion: Certain bacteria produce invasions that allow them to enter host cells, while immune cells can evade them by producing antiphagocytic factors like capsules.
Enzymatic Activity: Bacteria can more easily spread and absorb nutrients when host tissues are broken down by enzymes like lipases and proteases. Enzymatic Activity:

By dissolving host tissues, enzymes such as lipases and proteases facilitate the growth and uptake of nutrients by bacteria.

Biofilm Formation: Many pathogenic bacteria produce biofilms, which create a protective matrix that boosts antibiotic resistance, immune defenses, and persistence.

Quorum Sensing: Bacteria use chemical signals to coordinate group behaviors like toxin secretion and biofilm formation. [49]-[54]

Non-antibiotic anti-virulence approaches:
Microbiome Modulation and Probiotics:
Probiotics alter the gut microbiota, which strengthens immune defenses, produces antimicrobial peptides (bacteriocins), and creates competition with pathogens. [55]

Natural Substances as Antivirulence Agents:
Polyphenols, flavonoids, essential oils, and other compounds derived from plants exhibit anti- virulence and antimicrobial properties by inhibiting the formation of biofilms, quorum sensing, and the production of toxins. [56]

NSAIDs and Repurposed Substances:
The anti-virulence characteristics of some NSAIDs and repurposed drugs (statins, phenothiazines, etc.) include inhibiting bacterial adhesion, lowering the production of toxins, and preventing the formation of biofilms. It has also been demonstrated that antibiotics work in concert to combat bacteria that are resistant to multiple drugs (MDR). [57],[58]
MDR-targeting bacteriophages Bacteriophages either deliver anti-virulence genes or specifically lyse MDR bacteria, disrupting biofilms and causing clones that produce toxins. [59]

Nanoparticles and Antimicrobial Peptides:
Antimicrobial peptides (AMPs) break down bacterial membranes, inhibit the expression of virulence genes, and use nanoparticles to improve drug delivery and effectiveness so that resistant strains can be targeted without causing new resistance. [60]

Molecular Mechanisms of Action of Non-Antibiotic Anti-Virulence Agents: -
It is known that non-antibiotic anti-virulence agents work through a number of important mechanisms that limit the selection pressure for resistance by decreasing bacterial pathogenicity without necessarily killing the bacteria.[61]

Inhibition of Quorum Sensing:
Many substances, such as probiotics, natural substances, and bacteriophages, inhibit bacterial chemical communication (quorum sensing), which stops the coordinated expression of virulence genes involved in the production of toxins, the formation of biofilms, and motility. For example, it has been demonstrated that the fengycins generated by probiotic Bacillus species inhibit quorum sensing and lessen Staphylococcus aureus virulence.[62],[63]

Disruption of Biofilms
Biofilm structures are known to protect bacteria from antimicrobial agents and the host immune system. The bacteria may become more amenable to removal if specific natural substances and peptides hinder the formation of the biofilm matrix or encourage the biofilm's dispersion. Probiotics can also prevent the development of pathogen biofilms by modifying mucosal surfaces through competitive adhesion and the release of bioactive molecules.[64]

Adhesion blocking and competitive exclusion
Probiotics and some repurposed drug molecules work by occupying adhesion sites or altering host cell receptors to prevent pathogens from binding to host tissues.[65]

Modulation of the immune system
Probiotics trigger host immune responses, which include increased secretory IgA production, anti-inflammatory cytokine stimulation, and dendritic and macrophage activation. These effects enhance pathogen clearance without inducing undue inflammation.[66],[67]

Inhibition or Neutralization of Toxins
Certain natural substances and bacteriophages degrade or inhibit bacterial toxins, reducing tissue damage and pathogenicity.[67]
Direct Antimicrobial Actions without Death
Certain antimicrobial peptides and nanoparticles cause bacterial membrane damage or suppress the expression of virulence genes in order to disrupt virulence. The selective pressure for resistance is reduced because these effects happen at low concentrations that do not result in bacterial death. When taken as a whole, these mechanisms are known to offer promising approaches against bacteria that are resistant to multiple drugs by focusing on bacterial pathogenicity rather than viability. [68],[69]

Current clinical applications and research status: -
The majority of anti-virulence drugs, such as quorum-sensing inhibitors, biofilm disruptors, and virulence gene regulators, are still in the preclinical stage as of 2024–2025, and very few have progressed to human clinical trials. About 78% of the anti-virulence agents under study have shown efficacy in vitro, according to the VFDB database summary, but only four of these compounds have advanced to clinical evaluation. [70] Organic molecules like polyketides, phenylpropanoids, benzenoids, organ heterocycles, and organic acids and their derivatives make up the majority of these agents. [71] Widespread clinical application has not yet been realized despite significant research advancements over the past 20 years, and the majority of ongoing clinical trials are concentrated on addressing particular pathogen

virulence factors. [72] Furthermore, while small-molecule anti-virulence agents are still mostly in the early stages of development, the FDA has approved complex immunoglobulin-based medications with anti- virulence activity (such as Raxibacumab and Bezlotoxumab) for specific indications. [73] Advances in high-throughput screening technologies, computer-aided drug design, and a growing understanding of molecular targets—such as pilicides, salicylate synthase inhibitors, cholesterol-dependent cytolysin blockers, and agents active against hard-to-treat multidrug-resistant strains like MRSA and VRSA—continue to propel growth in this field.[74] Numerous substances, such as coumarin, ibuprofen, simvastatin, and nanoformulations like NM102, have shown encouraging results in preclinical models, and combination treatments with traditional antimicrobials are being assessed for safety profiles and synergistic effects. [75],[76]

FDA-Approved Anti-Virulence Therapies

Although most anti-virulence agents remain in preclinical or early clinical development, a few have received regulatory approval for specific indications. Bezlotoxumab is a human monoclonal antibody approved for the prevention of recurrent Clostridioides difficile infection. It acts by neutralizing toxin B, thereby reducing disease severity and recurrence. Raxibacumab is another monoclonal antibody approved for the treatment and prevention of inhalational anthrax. It binds to the protective antigen component of Bacillus anthracis toxin, preventing toxin entry into host cells. These agents demonstrate the clinical feasibility of anti-virulence strategies and support further development of therapies targeting bacterial pathogenic mechanisms rather than bacterial survival. [77]-[79]

Table 4. Comparison Between Conventional Antibiotics and Anti-Virulence Therapy

Feature	Conventional Antibiotics	Anti-Virulence Therapy	Reference
Primary Target	Bacterial growth or survival	Bacterial virulence factors	[80]
Mechanism of Action	Kills bacteria or inhibits growth	Reduces pathogenicity without killing bacteria	[81]
Resistance Development	High selective pressure	Lower selective pressure	[82]
Effect on Normal Microbiota	Often disrupts beneficial microbiota	Generally preserves microbiota	[83]
Spectrum of Activity	Broad or narrow spectrum	Usually target-specific	[84]
Risk of Resistance	Higher	Lower, but not completely eliminated	[85]
Immune System Role	Less dependent on host immunity	Works synergistically with host immune defenses	[86]
Examples	Penicillin, Ciprofloxacin, Vancomycin	Bezlotoxumab, Raxibacumab, Quorum-sensing inhibitors, Probiotics	[87]

Challenges and Future Directions for Anti-Virulence Therapies in Clinical Settings: -

It is still unclear how different virulence factors interact with different host environments due to complex molecular mechanisms. Since bacterial virulence is known to be multifactorial and frequently unique to both the pathogen and the host, it becomes more difficult to identify and validate targets for broad-spectrum therapeutic efficacy. Only a small number of anti-virulence compounds have progressed to clinical trials, despite the fact that many have shown effectiveness in vitro and in animal models. [88] There are currently no validated biomarkers that link the expression of virulence factors with the severity of the disease, standardized predictive models for pharmacokinetic and pharmacodynamic parameters, or ideal dosage.[89] There are currently no fully developed diagnostic methods that can accurately and quickly identify particular pathogens and their virulence profiles in patients. It is still difficult to effectively stratify patients for targeted therapy because the expression of some virulence factors differs depending on the bacterial strain, infection site, and disease state.[90] Resistance cannot be completely ruled out, even though ant virulence agents are thought to exert less selective pressure than traditional antibiotics, especially when administered for an extended period of time or as a monotherapy. [91]Combination therapy with traditional antibiotics and the development of agents that target conserved virulence mechanisms may help to reduce this risk. [92]

Approval procedures are delayed because regulatory pathways for antivirulence medications are still unclear. Current technological limitations limit the manufacturing and large-scale production of complex molecules like peptides and bacteriophages; therefore, additional advancements are necessary to ensure stable formulation and consistent production quality. [93],[94]

Advantages of non-antibiotic anti-virulence therapy include:

Decreased Selective Pressure for Resistance: Anti-virulence medications target bacterial pathogenic mechanisms that are necessary for disease causation but not for survival,which lowers the evolutionary pressure for resistance. As a result, resistance may develop more slowly than it would with conventional antibiotics.

Preservation of Normal Microbiota: Anti-virulence agents preserve the normal microbiota because they do not directly kill bacteria or deprive them of vital physiological processes. The beneficial microbial communities that offer defense against opportunistic infections are preserved in this manner.

Improvement of Host Immune Clearance: The host's innate immune systems are strengthened and infections can be eliminated more successfully by blocking virulence factors like toxins, adhesion molecules, and secretion systems.

Possible Lower Side Effects: When compared to the use of broad-spectrum antibiotics, these medications produce fewer off-target effects and cause less collateral damage to the host's immune system and microbiome because they do not kill bacteria in a broad manner.

Synergy with Antibiotics: Anti-virulence compounds can be used in conjunction with antibiotics to increase efficacy and lower dosage requirements. Antibiotic toxicity may be reduced and their lifespan increased through such synergistic interaction.

Target Specificity: To reduce unwanted effects on non-pathogenic bacterial populations, non-antibiotic anti-virulence medications can be made to target particular virulence mechanisms that are exclusive to pathogenic species.

With these benefits, ant virulence treatments are positioned as viable supplements or substitutes for traditional antibiotics in the fight against infections that are resistant to multiple drugs, while also preventing the development of resistance and preserving the health of the microbiome.[95]-[100]

Disadvantages of non-antibiotic anti-virulence therapy include:-

Clinical Impact of MDR Infections: Due to the scarcity of effective antibiotics, multidrug- resistant (MDR) infections have been linked to higher rates of treatment failure. Patients with MDR bacterial infections have been found to have longer durations of illness, higher rates of complications, and higher mortality. For example, it has been demonstrated that infections caused by MDR Pseudomonas aeruginosa, Klebsiella pneumoniae, and Acinetobacter baumannii have significantly higher mortality rates than infections caused by antibiotic-susceptible strains.

Prolonged Hospitalization - Patients infected with multidrug-resistant (MDR) organisms often need longer hospital stays. As a result, there is a higher chance of contracting more hospital-associated infections, and extended hospital stays put more strain on healthcare systems.

Increased Healthcare Costs- For the treatment of MDR infections, costly, last-resort antibiotics like colistin or carbapenems are frequently needed. Prolonged hospital stays, additional diagnostic testing, isolation procedures, and the provision of intensive care support all contribute to the overall economic burden.

Limited Treatment Options-Combination therapy or older, more toxic agents are frequently required when standard first-line antibiotics are rendered ineffective. Treatment becomes more complicated as a result, and serious side effects like ototoxicity or nephrotoxicity could occur.

Higher Risk of Complications- When effective therapy is delayed, MDR infections can lead to organ failure, sepsis, or metastatic infections. Catheter-associated infections, ventilator-associated pneumonia, and surgical site infections are particularly prevalent in these circumstances.

Challenges in Infection Control- In hospital settings, it is more challenging to eradicate MDR pathogens. Strict infection control measures, including isolation, cohorting, and improved hygiene protocols, must be put in place to prevent outbreaks of MDR organisms.

Public Health Threat- MDR infections contribute to the worldwide burden of antimicrobial resistance (AMR). Since effective antibiotics are necessary to prevent infections during procedures like surgery, chemotherapy, and organ transplantation, the efficacy of contemporary medical practices is jeopardized.

Vulnerable Populations- Elderly people, immunocompromised people, and critically ill patients are disproportionately affected by MDR infections. It is also known that pediatric populations are more vulnerable, especially those in neonatal intensive care units (NICUs) [101]-[108]

Refernce:-

Naghavi M, Murray CJ, Ikuta KS, Mestrovic T, Swetschinski L, Sartorius B. Global burden of antimicrobial resistance: essential pieces of a global puzzle–Authors' reply. The Lancet. 2022 Jun 25;399(10344):2349-50.

Hall CW, Mah TF. Molecular mechanisms of biofilm-based antibiotic resistance and tolerance in pathogenic bacteria. FEMS Microbiology Reviews. 2017;41(3):276-301.

Kumar V, Yasmeen N, Pandey A, Chaudhary AA, Alawam AS, Rudayni HA, Islam A, Lakhawat SS, Sharma PK, Shahid M. Antibiotic adjuvants: synergistic tool to combat multi-drug resistant pathogens. Front Cell Infect Microbiol 13 [Internet]. 2023.

Chinemerem Nwobodo D, Ugwu MC, Oliseloke Anie C, Al-Ouqaili MT, Chinedu Ikem J, Victor Chigozie U, Saki M. Antibiotic resistance: The challenges and some emerging strategies for tackling a global

menace. Journal of clinical laboratory analysis. 2022 Sep;36(9):e24655.

Marino A, Maniaci A, Lentini M, Ronsivalle S, Nunnari G, Cocuzza S, Parisi FM, Cacopardo B, Lavalle S, La Via L. The Global Burden of Multidrug-Resistant Bacteria. Epidemiologia. 2025 May 5;6(2):21.)

Dickey SW, Cheung GYC, Otto M. Different drugs for bad bugs: antivirulence strategies in the age of antibiotic resistance. Nature Reviews Drug Discovery. 2017;16(7):457-471.

Rasko DA, Sperandio V. Anti-virulence strategies to combat bacteria-mediated disease. Nature Reviews Drug Discovery. 2010;9(2):117-128.

hou S, Li X, Zhang T, et al. An integrated resource for exploring anti-virulence compounds. Nucleic Acids Res. 2025 Jan 5;53(D1):D871-D875.

Fleitas Martínez O, Cardoso MH, Ribeiro SM, et al. Recent Advances in Anti-virulence Therapeutic Strategies Against Bacterial Infections. Front Cell Infect Microbiol. 2019 Apr 1;9:74.

Rasko DA, Sperandio V. Anti-virulence strategies to combat bacteria-mediated disease. Nat Rev Drug Discov. 2010 Jan;9(2):117-28.

Dickey SW, Cheung GY, Otto M. Antivirulence strategies in the age of antibiotic resistance. Nat Rev Microbiol. 2017 Apr;15(4):358-370.

Fleitas Martínez O, Cardoso MH, Ribeiro SM, et al. Recent advances in anti-virulence therapeutic strategies with a focus on dismantling bacterial membrane microdomains, toxin neutralization, and biofilm inhibition. Frontiers in Cellular and Infection Microbiology. 2019;9:74.

World Health Organization. Antimicrobial Resistance Fact Sheet. Geneva: World Health Organization; 2024.

Allen RC, Popat R, Diggle SP, Brown SP. Targeting virulence: can we make evolution-proof drugs? Nature Reviews Microbiology. 2014;12(4):300-308.

Theuretzbacher U, Outterson K, Engel A, Karlén A. The global preclinical antibacterial pipeline. Nature Reviews Microbiology. 2020;18(5):275-285.

Bush K, Bradford PA. Epidemiology of β-lactamase-producing pathogens. Clinical Microbiology Reviews. 2020;33(2).

Li XZ, Plésiat P, Nikaido H. The challenge of efflux-mediated antibiotic resistance in Gram-negative bacteria. Clinical Microbiology Reviews. 2015;28(2):337-418.

Totsika M. Benefits and challenges of antivirulence antimicrobials at the dawn of the post-antibiotic era. Drug Delivery Letters. 2016;6(1):30-37.

Migone TS, Subramanian GM, Zhong J, et al. Raxibacumab for the treatment of inhalational anthrax. New England Journal of Medicine. 2009;361(2):135-144.

Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for prevention of recurrent Clostridioides difficile infection. New England Journal of Medicine. 2017;376(4):305-317.

Allen RC, Popat R, Diggle SP, Brown SP. Targeting virulence: can we make evolution-proof drugs?. Nature Reviews Microbiology. 2014 Apr;12(4):300-8.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. bmj. 2021 Mar 29;372.

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj. 2009 Jul 21;339.

Jpt H. Cochrane handbook for systematic reviews of interventions. http://www. cochrane-handbook. org. 2008.

Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, Harbarth S, Hindler JF, Kahlmeter G, Olsson-Liljequist BJ, Paterson DL. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clinical microbiology and infection. 2012 Mar 1;18(3):268-81.

Tacconelli E. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development.

Virulence factor. Wikipedia. https://en.wikipedia.org/wiki/Virulence_factor

Peterson JW. Bacterial Pathogenesis. In: Baron S, editor. Medical Microbiology. 4th edition. Galveston (TX): University of Texas Medical Branch at Galveston; 1996. https://www.ncbi.nlm.nih.gov/books/NBK8526/

Sharma AK, et al. Bacterial Virulence Factors: Secreted for Survival. Front Cell Infect Microbiol. 2016;6:215. https://pmc.ncbi.nlm.nih.gov/articles/PMC5243249/

Baba-Moussa L, Anani L, Scheftel JM, Couturier M, Riegel P, Haikou N, Hounsou F, Monteil H, Sanni A, Prévost G. Virulence factors produced by strains of Staphylococcus aureus isolated from urinary tract infections. Journal of hospital infection. 2008 Jan 1;68(1):32-8.

Zhou J. Mechanisms of Virulence Reprogramming in Bacterial Pathogens. Annu Rev Microbiol. 2023;77: 501-524.

Hughes D, Andersson DI. Evolutionary trajectories to antibiotic resistance. Annual review of microbiology. 2017 Sep 8;71(1):579-96.

Jabra-Rizk MA, Kong EF, Tsui C, Nguyen MH, Clancy CJ, Fidel Jr PL, Noverr M. Candida albicans pathogenesis: fitting within the host-microbe damage response framework. Infection and immunity. 2016 Oct;84(10):2724-39.

Jakobsen TH, van Gennip M, Phipps RK, Shanmugham MS, Christensen LD, Alhede M, Skindersoe ME, Rasmussen TB, Friedrich K, Uthe F, Jensen PØ. Ajoene, a sulfur-rich molecule from garlic, inhibits genes controlled by quorum sensing. Antimicrobial agents and chemotherapy. 2012 May;56(5):2314-25.

Li J, Jia T, Yang L. Targeting anti-virulence factor strategies of bacterial pathogens. Biosafety and Health. 2025 Feb 1;7(1):1-4.

Kalia VC, Patel SK, Kang YC, Lee JK. Quorum sensing inhibitors as antipathogens: biotechnological applications. Biotechnology advances. 2019 Jan 1;37(1):68-90.

Aggarwal M, Patra A, Awasthi I, George A, Gagneja S, Gupta V, Capalash N, Sharma P. Drug repurposing against antibiotic resistant bacterial pathogens. European Journal of Medicinal Chemistry. 2024 Dec 5;279:116833.

Kaplan JÁ. Biofilm dispersal: mechanisms, clinical implications, and potential therapeutic uses. Journal of dental research. 2010 Mar;89(3):205-18.

Singh B, Singh JP, Kaur A, Singh N. Phenolic composition and antioxidant potential of grain legume seeds: A review. Food research international. 2017 Nov 1;101:1-6.

Sawa T, Moriyama K, Kinoshita M. Current status of bacteriophage therapy for severe bacterial infections. Journal of Intensive Care. 2024 Nov 1;12(1):44.

Koo H, Allan RN, Howlin RP, Stoodley P, Hall-Stoodley L. Targeting microbial biofilms: current and prospective therapeutic strategies. Nature Reviews Microbiology. 2017 Dec;15(12):740-55.

Chadha J, Harjai K, Chhibber S. Repurposing phytochemicals as anti-virulent agents to attenuate quorum sensing-regulated virulence factors and biofilm formation in Pseudomonas aeruginosa. Microbial biotechnology. 2022 Jun;15(6):1695-718.

Silva LN, Zimmer KR, Macedo AJ, Trentin DS. Plant natural products targeting bacterial virulence factors. Chemical reviews. 2016 Aug 24;116(16):9162-236.

Lamont RJ, Koo H, Hajishengallis G. The oral microbiota: dynamic communities and host interactions. Nature reviews microbiology. 2018 Dec;16(12):745-59.

Park JS, Choi GS, Kim SH, Kim HR, Kim NK, Lee KY, Kang SB, Kim JY, Lee KY, Kim BC, Bae BN. Multicenter analysis of risk factors for anastomotic leakage after laparoscopic rectal cancer excision: the Korean laparoscopic colorectal surgery study group. Annals of surgery. 2013 Apr 1;257(4):665-71.

Ruan Q, Geng S, Yu J, Lu L, Liu Y, Chen J, Liao Q, Guo R. Microbial quorum sensing: Mechanisms, applications, and challenges. Biotechnology Advances. 2025 Oct 6:108733.

Mah TF, O'Toole GA. Mechanisms of biofilm resistance to antimicrobial agents. Trends in microbiology. 2001 Jan 1;9(1):34-9.

Marchant R, Banat IM. Biosurfactants: a sustainable replacement for chemical surfactants?. Biotechnology letters. 2012 Sep;34(9):1597-605.

Dehbanipour R, Ghalavand Z. Anti-virulence therapeutic strategies against bacterial infections: recent advances. Germs. 2022 Jun 30;12(2):262.

Cirit OS, Çaycı YT. Microbiology and Infectious Agents. InPrinciples of Nursing Infection Prevention Control: Introduction and global context of Infection Prevention and Control (Volume 1) 2025 May 13 (pp. 57-75). Cham: Springer Nature Switzerland.

Peterson JW. Bacterial Pathogenesis. In: Baron S, editor. Medical Microbiology. 4th edition. 1996. Available from: https://www.ncbi.nlm.nih.gov/books/NBK8526/

Sharma AK, et al. Bacterial Virulence Factors: Secreted for Survival. Front Cell Infect Microbiol. 2016;6:215. Available from: https://pmc.ncbi.nlm.nih.gov/articles/PMC5243249/

15.3:Virulence Factors. Microbiology (OpenStax), 2024 Apr 20. Available from: https://bio.libretexts.org/Bookshelves/Microbiology/Microbiology_(OpenStax)/15:_Microbial_Mechanisms_of_Pathogenicity/15.03:_Virulence_Factors

Type III Secretion and Pathogenicity Islands. Emerg Infect Dis. 2010 Dec 20. Available from: https://wwwnc.cdc.gov/eid/article/2/4/96-0403_article

Diard M, et al. Evolution of bacterial virulence. FEMS Microbiol Rev. 2017 Aug 31;41(5):679-693. Available from: https://academic.oup.com/femsre/article/41/5/679/3844166

Chandrasekaran P, et al. Effects of Probiotics on Gut Microbiota: An Overview. Front Microbiol. 2024;15:1289.

Petrariu OA, et al. Role of probiotics in managing various human diseases. Front Microbiol. 2024;15:1296447.

Raheem A, et al. Modulatory Effects of Probiotics During Pathogenic Infections. Pathogens. 2021;10(4):425.

Explorationpub. Mechanisms of action and health benefits of probiotics. Exploration of Drug Science. 2025.

Fleitas Martínez O, et al. Recent Advances in Anti-virulence Therapeutic Strategies. Front Cell Infect Microbiol. 2019;9:74.

Cegelski L, Marshall GR, Eldridge GR, Hultgren SJ. The biology and future prospects of antivirulence therapies. Nature Reviews Microbiology. 2008 Jan;6(1):17-27.

Barak TH, Eryilmaz M, Karaca B, Servi H, Kara Ertekin S, Dinc M, Ustuner H. Antimicrobial, anti-Biofilm, anti-quorum sensing and cytotoxic activities of

Thymbra spicata L. subsp. spicata essential oils. Antibiotics. 2025 Feb 11;14(2):181.

Chatterjee M, Anju CP, Biswas L, Kumar VA, Mohan CG, Biswas R. Antibiotic resistance in Pseudomonas aeruginosa and alternative therapeutic options. International Journal of Medical Microbiology. 2016 Jan 1;306(1):48-58.

Prabhakaran M, Prabakaran M, Kanagaraja A, Gopinath SC, Raman P. Disruption of quorum sensing and biofilm formation in Pseudomonas aeruginosa by plant-based O-methylated flavonoids. International Microbiology. 2025 Dec;28(8):3003-13.

Clatworthy AE, Pierson E, Hung DT. Targeting virulence: a new paradigm for antimicrobial therapy. Nature chemical biology. 2007 Sep;3(9):541-8.

Schroeder M, Brooks BD, Brooks AE. The complex relationship between virulence and antibiotic resistance. Genes. 2017 Jan 18;8(1):39.

Marra A. Can virulence factors be viable antibacterial targets?. Expert review of anti-infective therapy. 2004 Feb 1;2(1):61-72.

Fong W, et al. Gut microbiota modulation: a novel strategy for prevention. Nat Rev Gastroenterol Hepatol. 2020 Jun;17(6):350-364.

Liu Y, Wang J, Wu C. Modulation of Gut Microbiota and Immune System by Probiotics, Pre-biotics, and Post-biotics. Front Nutr. 2022 Jan 2;8:634897.

Zhou S, Liu B, Zheng D, Chen L, Yang J. VFDB 2025: an integrated resource for exploring anti-virulence compounds. Nucleic Acids Research. 2025 Jan 6;53(D1):D871-7.

Dighe SN, et al. Evaluation of novel compounds as anti-bacterial or anti-virulence agents. Front Cell Infect Microbiol. 2024;14:1370062.

Tran SL, et al. An anti-virulence drug targeting the evolvability protein Mfd. Nat Commun. 2025;16:236.

López-Lluch G, del Pozo-Cruz J, Sánchez-Cuesta A, Cortés-Rodríguez AB, Navas P. Bioavailability of coenzyme Q10 supplements depends on carrier lipids and solubilization. Nutrition. 2019 Jan 1;57:133-40.

Crawford JM, Clardy J. Bacterial symbionts and natural products. Chemical communications. 2011;47(27):7559-66.

Rather MA, Gupta K, Mandal M. Microbial biofilm: formation, architecture, antibiotic resistance, and control strategies. Brazilian Journal of Microbiology. 2021 Dec;52(4):1701-18.

Defoirdt T. Quorum-sensing systems as targets for antivirulence therapy. Trends in microbiology. 2018 Apr 1;26(4):313-28.

Wang J, et al. Proven anti-virulence therapies in combating methicillin-resistant and vancomycin-resistant S. aureus. Front Cell Infect Microbiol. 2024;14:1403219.

Hall-Stoodley L, Costerton JW, Stoodley P. Bacterial biofilms: from the natural environment to infectious diseases. Nature reviews microbiology. 2004 Feb;2(2):95-108.

Subramaniam G, Khan GZ, Sivasamugham LA, Wong LS, Kidd S, Yap CK. Antimicrobial and anti-biofilm activities of plant extracts against Pseudomonas aeruginosa-a review.

Donlan RM. Biofilms and device-associated infections. Emerging infectious diseases. 2001 Mar;7(2):277.

Duan K, Dammel C, Stein J, Rabin H, Surette MG. Modulation of Pseudomonas aeruginosa gene expression by host microflora through interspecies communication. Molecular microbiology. 2003 Dec;50(5):1477-91.

Kaufmann SH, Dorhoi A, Hotchkiss RS, Bartenschlager R. Host-directed therapies for bacterial and viral infections. Nature reviews Drug discovery. 2018 Jan;17(1):35-56.

El-Hawary SS, Sayed AM, Mohammed R, Hassan HM, Rateb ME, Amin E, Mohammed TA, El-Mesery M, Bin Muhsinah A, Alsayari A, Wajant H. Bioactive brominated oxindole alkaloids from the Red Sea sponge Callyspongia siphonella. Marine drugs. 2019 Aug 9;17(8):465.

Ong CJ, Elesho OE, Bramwell BB, Cabuhat KS, Bacalzo GD, Nuevo JJ, Fortaleza JA. Staphylococcus aureus: Antimicrobial resistance, quorum sensing, and antibiofilm approaches. European Journal of Microbiology and Immunology. 2025 Dec 16;15(4):195-209.

Hamid ME, Alamri F, Abdelrahim IM, Joseph M, Elamin MM, Alraih AM, Alammari F, Abdelrahim Sr IM, Alraih AH. Effects of antimicrobial flavonoids against representative bacteria and fungi: a review of the literature. Cureus. 2024 Jun 20;16(6).

Fetzner S. Quorum quenching enzymes. Journal of biotechnology. 2015 May 10;201:2-14.

Gupta PD, Birdi TJ. Development of botanicals to combat antibiotic resistance. Journal of Ayurveda and integrative medicine. 2017 Oct 1;8(4):266-75.

Furusawa M, et al. Current Clinical Laboratory Challenges to Widespread Adoption of Phage Therapy. Int J Mol Sci. 2025;26(11):6547.

Kumar V, et al. Pathogen virulence genes: Advances, challenges and future perspectives. Int J Mol Med. 2025 Aug 21;56(3):5614.

McCarthy M, Goncalves M, Powell H, Morey B, Turner M, Merrill AR. A structural approach to anti-virulence: A discovery pipeline. Microorganisms. 2021 Dec 4;9(12):2514.

Hentzer M, Givskov M. Pharmacological inhibition of quorum sensing for the treatment of chronic bacterial infections. The Journal of clinical investigation. 2003 Nov 1;112(9):1300-7.

Sharmin S, Rahaman MM, Sarkar C, Atolani O, Islam MT, Adeyemi OS. Nanoparticles as antimicrobial and antiviral agents: A literature-based perspective study. Heliyon. 2021 Mar 1;7(3).

Hmelo LR. Quorum sensing in marine microbial environments. Annual review of marine science. 2017 Jan 3;9(1):257-81.

Høiby N, Bjarnsholt T, Givskov M, Molin S, Ciofu O. Antibiotic resistance of bacterial biofilms. International journal of antimicrobial agents. 2010 Apr 1;35(4):322-32.

Robert III W, EricáBallard T. Inhibition and dispersion of proteobacterial biofilms. Chemical communications. 2008(14):1698-700.

Li J, Jia T, Yang L. Targeting anti-virulence factor strategies of bacterial pathogens. Biosafety and Health. 2025 Feb 1;7(1):1-4.

Martínez JL, Baquero F. Interactions among strategies associated with bacterial infection: pathogenicity, epidemicity, and antibiotic resistance. Clinical microbiology reviews. 2002 Oct;15(4):647-79.

Mookherjee N, Anderson MA, Haagsman HP, Davidson DJ. Antimicrobial host defence peptides: functions and clinical potential. Nature reviews Drug discovery. 2020 May;19(5):311-32.

Melander RJ, Melander C. The challenge of overcoming antibiotic resistance: an adjuvant approach?. ACS infectious diseases. 2017 Aug 11;3(8):559-63.

Murugayah SA, Gerth ML. Engineering quorum quenching enzymes: progress and perspectives. Biochemical Society Transactions. 2019 Jun 28;47(3):793-800.

Dickey SW, Cheung GY, Otto M. Different drugs for bad bugs: antivirulence strategies in the age of antibiotic resistance. Nature Reviews Drug Discovery. 2017 Jul; 16(7):457-71.

Stoitsova S, Paunova-Krasteva T, Dimitrova PD, Damyanova T. The concept for the antivirulence therapeutics approach as alternative to antibiotics: hope or still a fiction?. Biotechnology & Biotechnological Equipment. 2022 Dec 31;36(1):697-705.

Ghazaei C. Anti-virulence therapy against bacterial infections: mechanisms of action and challenges. J Kermanshah Univ Med Sci. 2021 Jan 1;25(3):e111808.

Rasko DA, Sperandio V. Anti-virulence strategies to combat bacteria-mediated disease. Nature reviews Drug discovery. 2010 Feb;9(2):117-28.

Totsika M. Benefits and challenges of antivirulence antimicrobials at the dawn of the post-antibiotic era. Drug Delivery Letters. 2016 Feb 1;6(1):307.

Popoff MR. Bacterial toxins, current perspectives. Toxins. 2020 Sep 4;12(9):570.

Moradali MF, Ghods S, Rehm BH. Pseudomonas aeruginosa lifestyle: a paradigm for adaptation, survival, and persistence. Frontiers in cellular and infection microbiology. 2017 Feb 15;7:39.

Goudarzi M, Navidinia M, Khadembashi N, Rasouli R. Biofilm matrix formation in human: clinical significance, diagnostic techniques, and therapeutic drugs.