Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/jptcp.v30i2.4702

# ENHANCING THE ACTIVITY OF ANTIMICROBIAL AGENTS

**Murad Abdullah Algarni[1*], Saleh Awad Alshamrani[2], Abdulrahman Atiah Alghamdi[3], Manal Abdulaziz Alsharif[4], Faisal Ahmed Albarqi[5], Fahad Mosakin Althubyani[6], Abdulaziz Saleh Abdullah Alghamdi[7], Ali Abdullah Alqarni[8], Emad Safar Alharbi[9], Razan Khalid Rambo[10]**

[1*]Pharmacist, Althager Hospital , Dr.Murad.Alqarni@Gmail.Com
[2]Pharmacy technician, Althager Hospital
[3]Pharmacy technician, Althager Hospital
[4]Pharmacy technician, Althager hospital
[5]Pharmacy technician, Althager hospital
[6]Pharmacist Assistant, Althager hospital
[7]Technician pharmacist, Eastern Jeddah Hospital
[8]Pharmacist, King Abdulaziz medical city
[9]Pharmacy technician, Eradh and mental health complex - mental services
[10]Pharmacist, King abdulaziz medical city

***Corresponding Author:** Murad Abdullah Algarni
*Pharmacist, Althager Hospital , Dr.Murad.Alqarni@Gmail.Com

**Abstract**
The rapid adaptability of bacteria to antibiotic-based therapy makes the development of effective medicines for infectious illnesses a complex and continuous process. Nevertheless, well-thought-out activity enhancers, such as antibiotic delivery systems, can boost the efficacy of the drugs now in use, defeating antimicrobial resistance and lowering the likelihood of fostering more bacterial resistance. The activity/delivery enhancers decrease adverse effects, increase tissue and biofilm penetration, improve medication absorption, and enable tailored antibiotic administration. In order to lessen the antibiotic adverse effects and improve formulation stability and effectiveness against bacteria that are resistant to several drugs, this review offers insights into a variety of antibiotic activity enhancers, such as polymer, lipid, and silver-based systems.

**Key words:** antimicrobial resistance, antibiotic, delivery systems, enhancers, nanoparticles.

## Introduction

Bacteria, fungi, viruses, and parasites are examples of microorganisms that cause infection-related diseases. Because of their advanced spread, high infection-related morbidity and mortality rates, and challenges in treating complicated diseases, pathogenic bacteria are among the most important public health concerns. Penicillin, the first "modern-day antimicrobial agent," was found in 1928 by Alexander Fleming. The subsequent two decades were dubbed the "golden era of antibiotics" because several more antibacterial drugs, including aminoglycosides and sulfonamides, were discovered during this time. These substances demonstrated revolutionary efficacy in treating infections that were previously fatal [1].

Numerous microorganisms may attach themselves to, endure, and flourish on both living and nonliving surfaces. Any kind of bacteria, fungus, virus, or even parasite could be among them. These give rise to a range of infectious diseases that result in a significant number of fatalities globally. Because of this, a robust field of study known as antimicrobial studies and research including their formulations and applicability has emerged since the discovery of antibiotics. Actually, around the start of the twenty first century, a number of antimicrobial medications evolved that reduced the morbidity and death of these microorganisms, ultimately resulting in their eradication [5].

Nowadays, the most important tools in the fight against infectious diseases are antibiotics. Nonetheless, the health of people and animals is seriously threatened by the spread of antibiotic resistance and the dearth of newly created antimicrobial medications. The main strategies for combating antimicrobial resistance include reasonable antibiotic usage. Numerous factors influence the efficiency of antibiotic treatment, but three key ones are the antibiotic itself, the target infection, and the bodily system of the patient [3].

One of the most significant developments in modern healthcare is the widespread use of antibiotics to treat a wide range of bacterial infections. However, because of their extensive use, the number of bacteria that are resistant to antibiotics is rising [4].

Ingredients known as antimicrobial agents have the power to either stop or eradicate microbial growth. In order to ensure food safety, these substances must often be incorporated into various food products. Examples of their use in the food industry include the inclusion of metals, fatty acids, essential oils, polyphenols, sodium nitrate, salts, and bacteriocins. Antibacterial agents typically work against bacteria by poreforming membranes, flocculating intracellular contents, blocking the synthesis of cell walls, changing the cytoplasmic membrane, binding nucleic acids, obstructing enzymatic activity, blocking the synthesis of nucleic acids, generating reactive oxygen species, interfering with the assimilation of nutrients, etc. These components are regarded by the food industry as crucial components of hurdle technology, which enhances food product safety and extends its shelf life [17].

AMR, or bacterial antimicrobial resistance, has become a major public health concern of the twenty-first century. It is caused by bacterial mutations that make antibiotics less effective. The Review on Antimicrobial Resistance, which was commissioned by the UK Government, estimates that by 2050, AMR might kill 10 million people yearly. Although some have questioned these forecasts, the WHO, several other organizations, and experts agree that the spread of AMR is a major issue that has to be tackled with a global, coordinated action plan. It is essential to have knowledge about the present scope of the bacterial antimicrobial resistance (AMR) burden, global trends, and the most common pathogen–drug combinations that contribute to this burden. If AMR continues unchecked, many bacterial infections may become far more deadly in the future than they are now [2].

**Literature review**

The development of numerous antimicrobial, antibacterial, antiviral, and antifungal agents has occurred within the last century. The organisms, on the other hand, have developed together with these antibiotics, and their resistance to these formulations has been created via feedback processes that have made the organisms resistant to the antibiotic agents that are currently in use. This is the reason behind the seemingly never-ending study and quest for novel formulations. Additionally, these organisms' mutations produce new infections, for which researchers must find even more inventive and cutting-edge antimicrobial medicines [5].

Antibiotics are used to treat infectious diseases on a large scale today; however, overuse of antibiotics over the past century because of prescriptions for unrelated infections and preventative use in agriculture has led to the natural selection of bacteria resistant to an increasing number of antibiotics

(AMR). Furthermore, the creation of novel antibiotics has become less appealing to pharmaceutical corporations due to their limited efficacious lifespan and competition from low-cost generics [1].
Any drug's usual antibacterial action can be explained in a number of ways. These include disrupting metabolic pathways, deactivating enzymes, blocking the creation of cell walls, blocking the synthesis of nucleic acids, deactivating protein synthesis, and interfering with the integrity of cell membranes. Even though a number of antibiotics have been discovered, created, and used thus far, they have significant drawbacks such as a limited range of antimicrobial action, safety concerns, poor medication absorption and effectiveness, toxicity, and other adverse effects [5].

There are now fatalities from previously treatable bacterial illnesses due to the emergence of bacterial strains that are concurrently resistant to various drugs. Bacterial infections are currently the second-leading cause of death worldwide, a situation made worse by drug resistance. According to a 2022 research, resistant bacterial infections caused around 5 million deaths worldwide in 2019 [2].

**Antimicrobial Resistance Mechanism**
The following pathways, known as intrinsic resistance mechanisms, may potentially result in resistance in bacteria due to their innate capacity to survive antibiotic treatment: 1-Drug permeability/uptake is reduced; 2-Biofilm development reduces the sensitivity of individual bacteria to antibiotic action; 3-Antibiotics are inactivated; 4-Enzymatic degradation occurs; and 5-Overexpression of efflux pump proteins occurs. A frequent source of acquired resistance, in addition to inherent resistance, is drug target mutations and horizontal gene transfer between species by transformation, transduction, or conjugation [1].

Gram-negative bacteria have an extra barrier on top of their outer membrane that stops antibiotics from penetrating them; this is a common intrinsic resistance mechanism that both Gram-positive and Gram-negative bacteria share. The two main strategies for combating antimicrobial resistance are the creation of novel antibiotics with wide modes of action or the use of delivery technologies to increase the effectiveness of currently available antimicrobial medicines [1].

**Antimicrobial agents' activity enhancers**
Modern Antimicrobial Agents
In order to be effective against multidrug-resistant (MDR) bacteria, new therapeutic medicines against pathogenic bacteria must also have a low potential for resistance development. There are two types of antimicrobial agents: natural agents and synthetic chemicals. Curcumin, which is taken from Zingiberaceae medicinal plants, is one example of a natural antibacterial agent that is grown from living organisms, such as filamentous saprophytic microorganisms. Another class of naturally occurring antibacterial agents are bacteriophages, which are DNA/RNA viruses that infect bacteria. Since practically all classes of current antibiotics are derived from natural molecules, synthetic antimicrobial substances, which are created via entirely synthetic chemical methods, synthetic biology, and genetic engineering, are still in the early phases of development [6].

Certain groups of antimicrobial agents can be entirely manufactured or obtained from nature, such as antimicrobial peptides (AMPs). AMPs are frequently extracted from plants, animals, including humans, and microbes (such as bacteria, fungus, and protozoa). For instance, there is a natural source of bacteriocin, ribosomal AMPs produced by a strain of Pediococcus acidilactici; on the other hand, GLK-19 is a synthetic peptide that exhibits broad-spectrum antibacterial action against both methicillin-resistant Staphylococcus aureus (MRSA) USA-300 and Escherichia coli [7].

AMP sequences are composed of five to fifty amino acids, typically arranged in a l-configuration, and frequently take the form of α-helices, β-sheets, or a combination of both. Because of their high efficacy, quick sterilization, small molecular weight (~500–5000 Dalton), suitable thermal stability,

and minimal immunogenicity, AMPs are appealing antimicrobial agents. However, despite these benefits, new AMPs have not been successful in receiving FDA approval as antibiotics [8].
To cling to and interact with the negatively charged bacterial cell surface membrane, the majority of AMPs contain net positive charges. Cell death results from this interaction's breakdown of the membrane's integrity and eventual rupture of the cell membrane. However, peptidic antimicrobial drugs are easily degraded, attach to serum proteins due to their cationic and amphiphilic character, and are quickly removed from circulation in the bloodstream. This membrane action, however, frequently also causes collateral damage to mammalian cells [7].

**Delivery Systems**

Delivery systems are typically made to increase the bioavailability of drugs, protect cargo from extracellular degradation, increase the half-life of antibiotics in plasma to prolong systemic drug circulation, enable sustained antibiotic release, and provide site-specific targeting. Delivery systems have the ability to simultaneously decrease toxicity and minimize the buildup of antibiotics in healthy host tissue [9].

Delivery mechanisms frequently boost the effects of antimicrobial agents. Effectiveness of the delivery mechanism is largely dependent on the drug incorporation approach. Stable conjugates can be formed through chemical conjugation, but the chemical linkages between the medication and carrier can also lessen the biological action of antimicrobial medicines. Additionally, these conjugates could have ineffective drug release [10].

**Nanomaterials in Antibiotic Delivery**

When used as antimicrobial agents or as vehicles to encapsulate antibiotics, nanomaterials can exhibit antibacterial activity. For instance, metal nanoparticles can increase the antimicrobial effectiveness of antibiotics by changing the metabolic activity of bacteria, including Gram-positive (Staphylococcus aureus) and Gram-negative (Escherichia coli) species. Several biological pathways can be addressed using nanoparticles. Therefore, antimicrobial activity tests should be performed on the materials used to administer antibiotics [11].

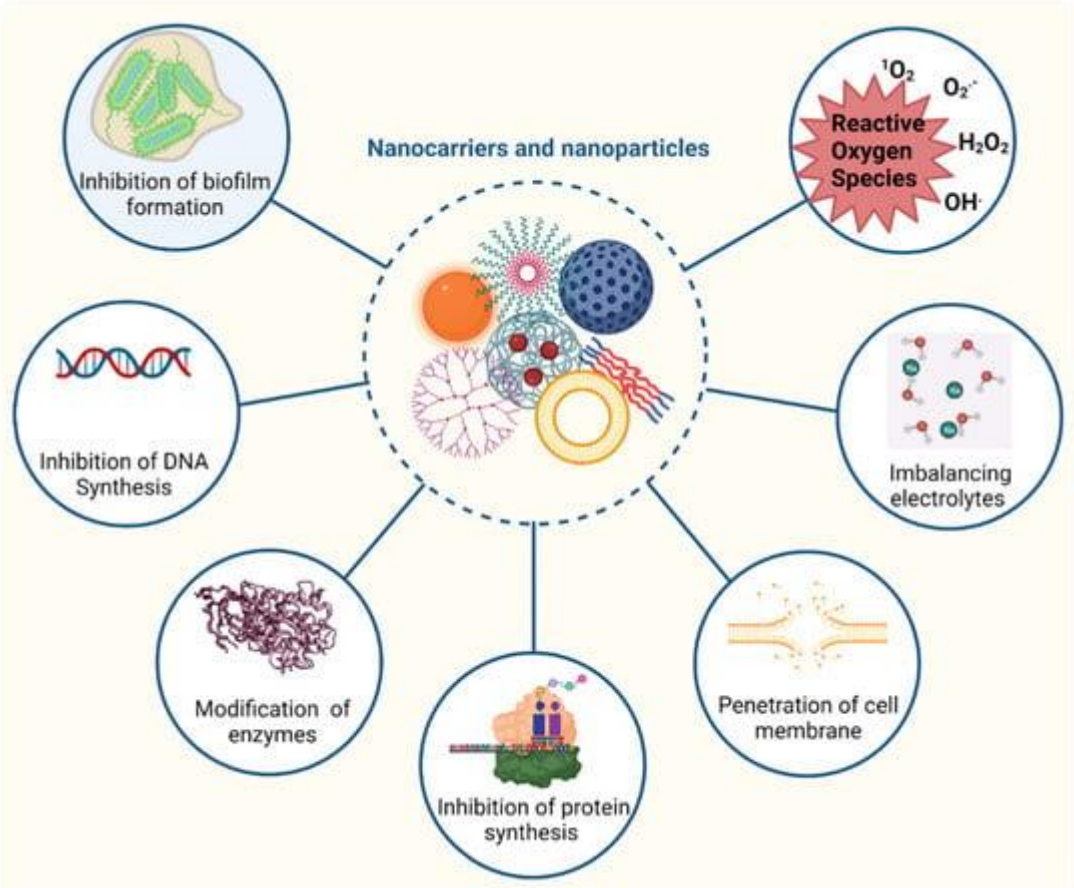


**Figure (1)** The most common mode of actions of antibiotics loaded in nanoparticles [1].

**Polymeric Delivery Systems**

High molecular weight substances are called polymers, and they are typically made up of one or more structural units linked by covalent connections. They quickly aggregate into nanostructures in water, mostly because of their framework's hydrophobic/hydrophilic properties. Polymer-based nanostructures can combine a number of structural functions and are often very biocompatible and stable in biological settings [12].

The use of polymeric systems in the development of antibiotics offers the possibility of creating nanobiotics with regulated drug release, better pharmacokinetics, and increased antibacterial activity. Hydrophilic antibiotics can be added to the inner reservoir of polymeric vesicles, while antibiotics with low water solubility can be put into the membrane or core of the micelles. Furthermore, water-soluble compounds, including cationic antimicrobial peptides, can be loaded into the core of micelles by modifying the block copolymer's core-forming region [13].

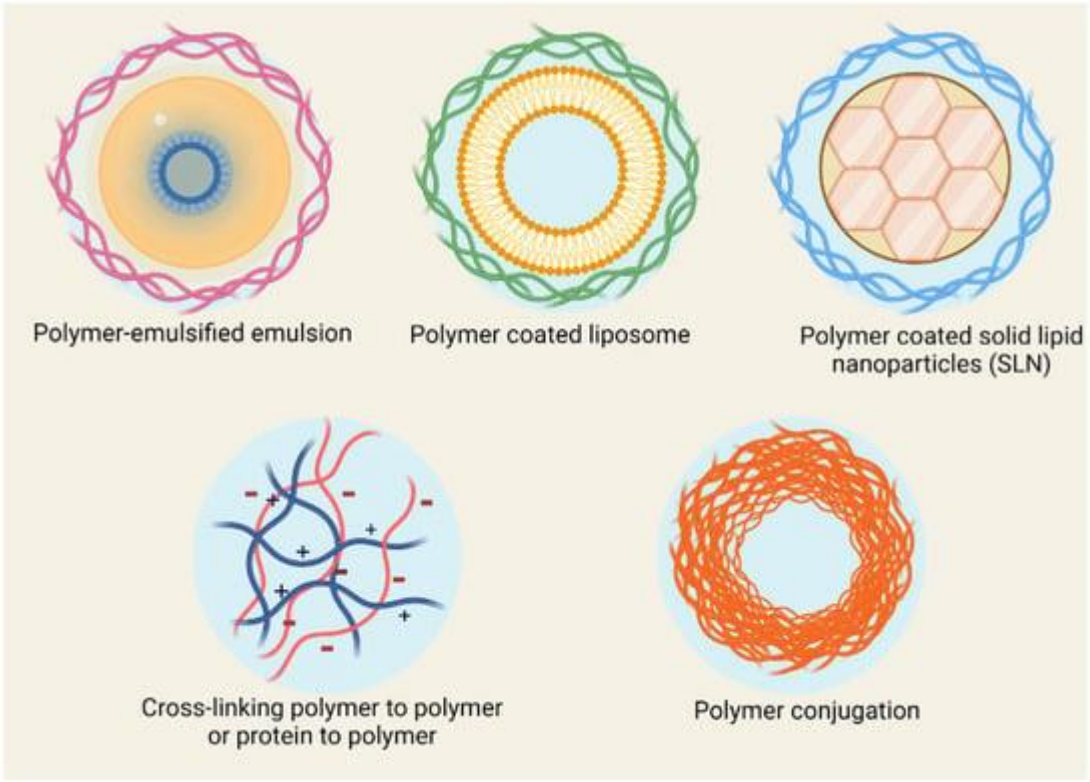


**Figure (2)** Polymer-based antibiotic delivery systems [12].

Bacterial cell envelopes are formally anionic due to the presence of teichoic acid and lipoteichoic acid in the case of Gram-positive bacteria, and liposaccharides and phospholipids in the case of Gram-negative bacteria. Catalytic polymers seem to primarily interact with this structure through electrostatic interactions. Bacterial mortality results from this destabilizing local neutralization of charge, which also appears to enhance the cell membrane's permeability. M. tuberculosis has a waxy, lipid-rich membrane that facilitates both cationic and hydrophobic interactions between polymers and the bacteria. Hydrophobic interactions are thought to be a crucial mechanism by which antimicrobial polymers can eliminate encapsulated viruses, including SARS-CoV-2, SARS coronavirus, Ebola virus, HIV, influenza virus, and so on. Epistolar membranes are also shielded from these viruses [14].

Xu et al. addressed fungal biodeterioration in the paper-making process by examining the antifungal activity of poly(borneol acrylate)s and developing a non-toxic antifungal covering. Ammonium persulfate was used as an initiator to generate poly (borneol acrylate) in methanol at 70 °C after it had been dissolved in DCM and sprayed. After that, paper was sprayed with the polymer. A. Niger and Penicillium sp., two fungi that can quickly spread by fungal spores and readily colonies the surfaces of most materials, were used to test the "polymer paper's" antifungal effectiveness. Consequently, the development of antifungal coatings depends on inhibition to prevent the transmission of fungal spores. Sporadic spores were the only growth on the 10% and 15% poly (borneol acrylate) coated papers following an eight-day incubation period of the polymer coated papers with fungi. Furthermore, only a few spores were visible on the surface and virtually no sporangia or hypha were seen in scanning electron microscopy (SEM) pictures. The antifungal mechanism is not easily explained; however, it is likely because of the hydrophobic property of the polymer, which prevented the fungi from adhering to the surface and preventing the transmission of fungal spores [14].

Hydrogels intended for gynecological treatments are made from both natural and synthetic polymers with thermoresponsive qualities. Amphiphilic copolymers of poly (ethylene oxide) and poly (propylene oxide) blocks were used to create hydrogels for gynecological therapy. These hydrogels were used to deliver synthetic antimicrobial medicines, including amoxicillin, metronidazole,

clotrimazole, and amphotericin, under controlled conditions. Amoxicillin is an antibacterial medication, however clotrimazole and amphotericin demonstrated antifungal efficacy. Metronidazole exhibits antibacterial and anti-Trichomonas vaginalis action, giving it a broader spectrum of action against microorganisms [15].

Without adding common anti-infection medications, careful selection of the hydrogel's constituent components can ensure the development of a therapeutic platform with antimicrobial action. In this industry, chitosan is the gold standard. It is widely recognized that it exhibits antimicrobial activity against fungi that are harmful to humans, including Candida and Gram-negative bacteria. Because of interactions between negatively charged cell surface proteins and protonated amine groups in chitosan, the antifungal activity may be due to pathogen membrane disruption and intracellular component leaking [15].

**Lipid-Based Nanostructures**

The distinct characteristics of lipid-based nanocarriers are their biodegradability, biocompatibility, and variety of physiochemical states. Liposomes, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), and nanoemulsions are a few of the lipid-based nanostructures that have been created. By using these nanostructures, pharmaceuticals that are poorly soluble in water or permeable can have their bioavailability increased, and the distribution of bioactive substances can be improved. Liposomes are lipids that are amphiphilic, meaning they may ensnare both hydrophilic and hydrophobic molecules. They are closed vesicles. With droplet sizes ranging from 20 to 600 nm, nanoemulsions are commonly categorized as either water-in-oil (W/O) or oil-in-water (O/W) dispersions stabilized by a surfactant molecule or interfacial film. The properties of the antimicrobial agent, the nanomaterial, and their use are frequently linked to the capability of the nanostructured system [16].

The liposome structure is suitable for encapsulating many bioactive substances, such as naturally occurring antimicrobials. However, the thermodynamic instability of these structures makes them prone to aggregation or degradation, which places restrictions on the viability of bioactive encapsulation. Several research recommend using biopolymers as coating materials to get over the liposome stability restrictions. Generally speaking, biopolymers can contribute to particle stabilization by altering the liposome surface via covalent or non-covalent interactions. Therefore, adding biopolymers—such as proteins, polysaccharides, and their derivatives—represents a viable tactic for enhancing liposome performance and increasing their stability, protection, and usefulness. Aside from starch, alginate, and pectin, chitosan is one of the most often utilized biopolymers for coating liposomes [16].

**Solid lipid nanoparticles (SLNs) loaded with antimicrobials**

Crystal structures called SLNs are organized in nanocarriers. SLNs are primarily made from O/W emulsions, in which the oil (liquid lipid) has been replaced with a solid lipid that forms a crystalline physiological lipid distributed in water or in an aqueous surfactant solution. This allows SLNs to maintain their solid structure at ambient and human body temperatures. Since the mobility of a bioactive component in solid lipid structures is substantially less than that of liquid lipid, the substitution of solid lipid for oil signifies a major breakthrough in the attainment of controlled bioactive release. Two traditional techniques for creating SLNs are hot homogenization and cold homogenization. To put it briefly, temperatures higher than the melting point of lipids are typically used for hot homogenization. Using a high shear mixing instrument, a pre-emulsion of the bioactive-loaded lipid melt and an aqueous emulsifier phase is achieved [17].

The pharmaceutical and clinical sciences are where SLNs are most frequently used to nanoencapsulate antimicrobial medicines. In these domains, antibacterial-loaded SLNs are mostly utilized to kill infectious bacteria, especially those that have formed biofilms in various body sections. A biofilm is a population of microorganisms that form sticky films on surfaces, interfaces, and between themselves. Compared to free forms of bacteria, the live bacteria in biofilms can have a

1000-fold higher resistance to antibacterial agents. When SLNs come into contact with biofilms, they concentrate antibacterial compounds, and their roughness—also referred to as nano-roughness—prevents biofilms from adhering to internal body surfaces. This is essentially how SLNs deal with biofilms. Furthermore, the destruction of biofilms is significantly aided by the charge of SLNs. Given that exopolysaccharide is the primary substance around biofilms [17].

**Silver-Based Systems Antimicrobial enhancers**

It has long been known that silver, when present in bulk (i.e., in its metallic form and in high numbers), demonstrates potent antibacterial properties against a wide variety of microbes. The emergence of nanotechnology and the unprecedented rise in multi-drug resistant bacteria have led scientists and industries worldwide to concentrate their expertise on the synthesis and application of silver as nanoparticles (NPs, i.e., molecules, structures, and substances with at least one dimension between 1 and 100 nm). Furthermore, Ag NPs have demonstrated efficacy in eliminating strains that are resistant to many drugs [18].

Regarding bacterial infection, metallic silver in a variety of forms and sizes demonstrated excellent potential. Ag has a strong affinity for nitrogen- and sulfur-containing intracellular and extracellular macromolecules, including proteins and nucleic acids. As a result, common cell functions like respiration and cell division would be impacted, ultimately leading to the death of the bacterium. Ag nanostructures have antibacterial efficacy that varies with size. The antibacterial efficacy increases with Ag nanoparticle size [19].

Many mechanisms of action have been thoroughly discussed thus far to explain silver's antibacterial activity. To date, nevertheless, the theory that is most frequently accepted is ion-mediated death, which is based on the exposure of bacteria to silver ions. According to this process, a key factor influencing how effective silver is against bacteria is the creation and release of silver ions. It has been shown that the absence of silver ions, which prevent silver from oxidizing to Ag(I) in media deficient in oxygen, causes silver nanoparticles to lose their antibacterial action in anaerobic conditions. The bactericidal effect of silver ions is dependent on the generation of reactive oxygen species (ROS), such as superoxide and peroxide anions. These oxygen-containing species have demonstrated an impressive capacity to limit the growth of bacteria by preventing the synthesis of the proteins required to produce adenosine triphosphate (ATP), a crucial source of energy for bacteria [18].

**Silver-Based MOFs**

Pure Ag-MOFs are three-dimensional materials made by certain methods (hydrothermal reaction, in-situ growth, etc.) that have silver acting as the metal nodes and organic linkers. MOFs are mostly used as "reservoirs" of Ag cations to ensure the regulated release of metal ions. The antibacterial activity of MOFs is higher when silver is present than when commercial silver nanoparticles are used. The MOF system can control how quickly silver is released and avoid the toxicity that comes with too fast a release. MOFs can be made to behave more antibacterially or to create more synergies by loading antimicrobial chemicals onto pure Ag-MOFs or by adding certain modifiers [19].

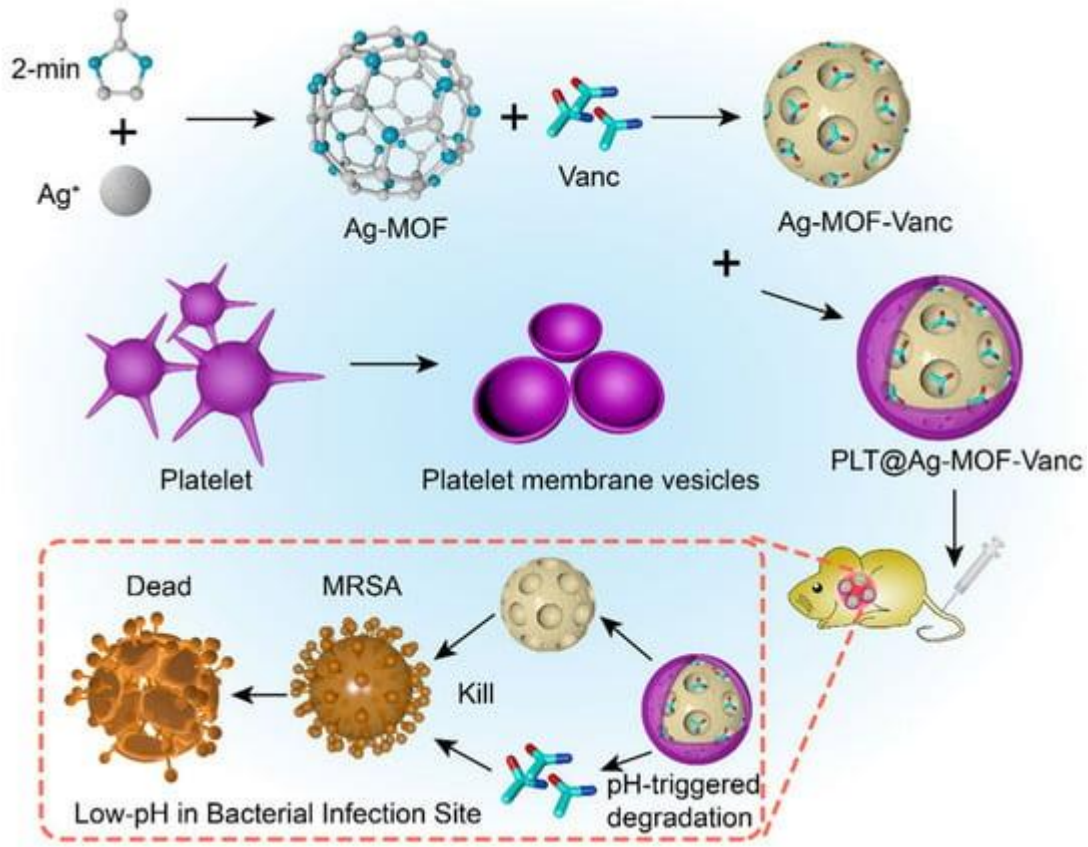


**Figure (3)** Schematic diagram of PLT@ Ag-MOF-Vanc in the treatment for a MRSA infection [19].

Through pH manipulation, the MOF-13 can release silver ions and pharmaceuticals to prevent an early release of drug into the circulatory system. With a minimum inhibitory concentration (MIC) of 0.5 μg mL−1, the MOF-13 showed a definite inhibitory effect against MRSA, outperforming both Ag-MOF-Vanc and vancomycin on their own. Among the possible synergistic reactions between physics and chemistry that underpin the antibacterial mechanism are the targeting of MRSA via PLTm, the disruption of intracellular bacterial metabolism, the catalytic effect in the production of ROS, the damage of cell membrane integrity, and the inhibition of biofilm formation [19].

## Conclusion

In the continuous fight against infectious illnesses, increasing the action of antimicrobial drugs is essential. Scientists have improved the effectiveness of antimicrobial therapies significantly via creative research and technical breakthroughs. In order to tackle elusive diseases and overcome antimicrobial resistance, strategies including combination therapy, drug delivery methods, and the discovery of new antimicrobial agents have showed promise. Working together, researchers, doctors, and legislators will be essential to advancing innovation and putting antimicrobial stewardship initiatives into action. Researchers may work together to increase the activity of antimicrobial agents and protect public health for future generations by prioritizing research funding, raising antimicrobial awareness, and fostering international collaboration.

## References

1. Skwarczynski M, Bashiri S, Yuan Y, Ziora ZM, Nabil O, Masuda K, et al. Antimicrobial activity enhancers: Towards smart delivery of antimicrobial agents. Antibiotics. 2022 Mar 18;11(3):412. doi:10.3390/antibiotics11030412
2. Murray CJ, Ikuta KS, Sharara F, Swetschinski L, Robles Aguilar G, Gray A, et al. Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. The Lancet. 2022 Feb;399(10325):629–55. doi:10.1016/s0140-6736(21)02724-0

3. Li J, Xie S, Ahmed S, Wang F, Gu Y, Zhang C, et al. Antimicrobial activity and resistance: Influencing factors. Frontiers in Pharmacology. 2017 Jun 13;8. doi:10.3389/fphar.2017.00364
4. Borselli D, Blanchet M, Bolla J, Muth A, Skruber K, Phanstiel O, et al. Motuporamine derivatives as antimicrobial agents and antibiotic enhancers against resistant gram-negative bacteria. ChemBioChem. 2017 Jan 18;18(3):276–83. doi:10.1002/cbic.201600532
5. Kale SN, Kitture R, Ghosh S, Chopade BA, Yakhmi JV. Nanomaterials as enhanced antimicrobial agent/activity-enhancer for transdermal applications: A Review. Antimicrobial Nanoarchitectonics. 2017;279–321. doi:10.1016/b978-0-323-52733-0.00011-2
6. Kim B, Kim E, Yoo Y-J, Bae H-W, Chung I-Y, Cho Y-H. Phage-derived antibacterials: Harnessing the simplicity, plasticity, and diversity of phages. Viruses. 2019 Mar 18;11(3):268. doi:10.3390/v11030268
7. Jaumaux F, P. Gómez de Cadiñanos L, Gabant P. In the age of synthetic biology, will antimicrobial peptides be the next generation of antibiotics? Antibiotics. 2020 Aug 6;9(8):484. doi:10.3390/antibiotics9080484
8. Fadaka AO, Sibuyi NR, Madiehe AM, Meyer M. Nanotechnology-based delivery systems for antimicrobial peptides. Pharmaceutics. 2021 Oct 26;13(11):1795. doi:10.3390/pharmaceutics13111795
9. Yeh Y-C, Huang T-H, Yang S-C, Chen C-C, Fang J-Y. Nano-based drug delivery or targeting to eradicate bacteria for infection mitigation: A review of recent advances. Frontiers in Chemistry. 2020 Apr 24;8. doi:10.3389/fchem.2020.00286
10. Khan H, Shukla RN, Bajpai AK. Genipin-modified gelatin nanocarriers as swelling controlled drug delivery system for in vitro release of Cytarabine. Materials Science and Engineering: C. 2016 Apr;61:457–65. doi:10.1016/j.msec.2015.12.085
11. Chatzimitakos TG, Stalikas CD. Qualitative alterations of bacterial metabolome after exposure to metal nanoparticles with bactericidal properties: A comprehensive workflow based on 1H NMR, UHPLC-HRMS, and metabolic databases. Journal of Proteome Research. 2016 Aug 3;15(9):3322–30. doi:10.1021/acs.jproteome.6b00489
12. Sung YK, Kim SW. Recent advances in polymeric drug delivery systems. Biomaterials Research. 2020 Jun 6;24(1). doi:10.1186/s40824-020-00190-7
13. Rezaei N, Hamidabadi HG, Khosravimelal S, Zahiri M, Ahovan ZA, Bojnordi MN, et al. Antimicrobial peptides-loaded smart chitosan hydrogel: Release behavior and antibacterial potential against antibiotic resistant clinical isolates. International Journal of Biological Macromolecules. 2020 Dec;164:855–62. doi:10.1016/j.ijbiomac.2020.07.011
14. Haktaniyan M, Bradley M. Polymers showing intrinsic antimicrobial activity. Chemical Society Reviews. 2022;51(20):8584–611. doi:10.1039/d2cs00558a
15. Gosecka M, Gosecki M. Antimicrobial polymer-based hydrogels for the intravaginal therapies—engineering considerations. Pharmaceutics. 2021 Sept 2;13(9):1393. doi:10.3390/pharmaceutics13091393
16. Pinilla CM, Lopes NA, Brandelli A. Lipid-based nanostructures for the delivery of natural antimicrobials. Molecules. 2021 Jun 11;26(12):3587. doi:10.3390/molecules26123587
17. Yousefi M, Ehsani A, Jafari SM. Lipid-based nano delivery of antimicrobials to control food-borne bacteria. Advances in Colloid and Interface Science. 2019 Aug;270:263–77. doi:10.1016/j.cis.2019.07.005
18. Bonilla-Gameros L, Chevallier P, Sarkissian A, Mantovani D. Silver-based antibacterial strategies for healthcare-associated infections: Processes, challenges, and regulations. an Integrated Review. Nanomedicine: Nanotechnology, Biology and Medicine. 2020 Feb;24:102142. doi:10.1016/j.nano.2019.102142
19. Zhang W, Ye G, Liao D, Chen X, Lu C, Nezamzadeh-Ejhieh A, et al. Recent advances of silver-based coordination polymers on antibacterial applications. Molecules. 2022 Oct 23;27(21):7166. doi:10.3390/molecules27217166