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Targeted Drug Delivery with Nano-Antibiotics to Mitigate Antibiotic-Related Adverse Effects and Mortality

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ABSTRACT: Antibiotics have revolutionized modern medicine over the last century, saving millions of lives and extending the average human lifespan. Twenty percent of people who receive antibiotics in the hospital experience at least one side effect. These can range from mild gastrointestinal irritation, skin, musculoskeletal, cardiac, and neurologic side effects to severe life-threatening events such as anaphylactic shock, Stevens-Johnson Syndrome, or *Clostridium difficile* infections. Antibiotic resistance is another global issue that is responsible for millions of deaths. Antibiotic resistance occurs when bacteria develop resistance to antibiotics bioengineered to kill them. Among bacteria that have developed ways to evade antibiotics' effectiveness are Methicillin-Resistant *Staphylococcus aureus, Escherichia coli, Mycobacterium tuberculosis*, and *Pseudomonas Aeruginosa*. Nano-antibiotics are being investigated to utilize antibiotics efficiently and reduce antibiotic resistance. Nano-antibiotics are either nanoparticles that naturally have antibacterial properties or traditional antibiotics that are packaged inside specialized nanoparticles. The unique properties of nanoparticles facilitate targeted, controlled drug delivery, thereby enhancing the bioavailability of the drugs. Nanotechnology has shown promising results in the treatment and prevention of *Clostridium difficile* infections. This research paper reviews antibiotic resistance and the improvement of antibiotic delivery using nanotechnology to reduce antibiotic-related adverse effects and mortality.

KEYWORDS: Materials Science, Nanomaterials, Nano-antibiotics, Targeted Delivery.

Introduction

Antibiotic resistance occurs when bacteria develop the ability to combat the drugs engineered to kill them. According to the CDC's 2019 Antibiotic Resistance Threat Report, more than 2.8 million antibiotic-resistant infections occur each year in the United States, and more than 35,000 people die as a result.[1]

According to a report by the World Health Organization, drug-resistant diseases could force up to 24 million people into poverty by 2030. Additionally, drug-resistant diseases could cause 10 million fatalities annually by 2050. If no mitigation or prevention strategies are available, antimicrobial resistance (AMR) can become a leading cause of death, even surpassing cancer by the year 2050. In addition to increased mortality, antimicrobial resistance increases the chance of secondary infection, making many medical procedures riskier. Antibiotic resistance is predicted to cost an additional $1 to $ 3.4 trillion in healthcare costs by 2050.[2]

Clostridium difficile is a bacterial infection that occurs when antibiotics are used to treat other infections. Antibiotic use causes a temporary disruption of normal gut flora, which allows *C. difficile* endospores to germinate and proliferate, resulting in a gut infection.[3] According to the Mayo Clinic, the symptoms range from mild to severe diarrhea, and it can be life-threatening in extreme cases.[4] If this infection is added to the CDC data, the total number of infections in the US per year exceeds 3 million infections per year, and the number of deaths exceeds 48,000 per year, making *C. difficile* the bacterium with the highest fatality rate due to antimicrobial resistance.[1]

A landmark study published in *The Lancet* forecasts that antimicrobial resistance (AMR) could be associated with the death of 169 million people from 2025 to 2050 if no preventive measures are taken. From now to 2050, yearly deaths from antibiotic-resistant infection are expected to rise to over a million, with 1.91 million deaths being estimated in 2050. The regions most likely to be affected are South Asia, Southeast Asia, and sub-Saharan Africa. These areas experience limited access to medical resources and lack proper regulation regarding the use of antibiotics. However, new and innovative drugs against gram-negative bacteria (labeled by the World Health Organization as the biggest threat to human health) could avert an estimated 11.1 million deaths. In addition to improved medications to treat antimicrobial-resistant bacteria, other strategies, such as infection prevention, vaccination, decreasing inappropriate use of antibiotics in farming and humans, could save an estimated 93 million deaths by 2050.[5]

Due to the detrimental outcomes of antimicrobial resistance on humanity, scientists are working on finding innovative prevention and treatment strategies to reduce the fatalities associated with antibiotic resistance. This will improve health outcomes in developing countries and provide valuable insight into the prevention of the antimicrobial crisis in the future.

Nano-antibiotics are currently being explored to reduce antibiotic resistance. Nano-antibiotics are conventional antibiotics that are encapsulated in specifically developed nanoparticles called nanocarriers. Many nanoparticles have intrinsic antibacterial activity. Utilizing their unique chemical properties, nanocarriers can deliver antibiotics to specific bacterial target sites via various mechanisms.[6] Many research studies have

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demonstrated promising results of nano-antibiotics in the prevention and treatment of drug-resistant diseases. The implementation of effective prevention strategies and the discovery of efficient nano-antibiotics have the potential to reduce mortality associated with infectious diseases.

However, determining the specific material for encapsulation, its bioavailability, biocompatibility, degradability, specificity for individual bacteria, and long-term safety are some challenges that new nanotechnology will have to overcome. The objective of this literature review is to provide valuable insight into the potential use of nanotechnology in developing nano-antibiotics to reduce antibiotic resistance, antibiotic-associated adverse effects, and mortality, as well as prevention strategies for *C. difficile*.

Methodology

The primary objective of this study was to investigate whether nano-antibiotics can be utilized to mitigate antimicrobial resistance and antibiotic-associated adverse effects. This research paper is a literature review of multiple peer-reviewed research articles and studies. The qualitative method of analysis was employed in this research paper to explore and investigate innovative prevention strategies for antibiotic resistance using nanoparticles. To complete this method of analysis, numerous articles were reviewed. Articles were selected based on their publication in peer-reviewed journals or reputable medical organizations, their relevance to antimicrobial resistance, the current state of nano-antibiotic research in combating antimicrobial resistance, antibiotic encapsulation by nanoparticles, *C. difficile* prevention, and the clarity of their methodologies. Based on study design, sample size, and experimental controls, each study was evaluated for any conflicting results. Studies lacking methodological detail or relevance to the research focus were excluded. Potential research biases and contradicting information were removed in part or in their entirety. Further research was conducted on the research gap: prevention of *C. difficile*, including the bacterium's pathophysiology, clinical features, diagnosis, and prevention strategies. No physical research or materials were used in this research paper, except for credible online resources such as the World Health Organization (WHO), Mayo Clinic, National Institutes of Health (NIH), and the University of Minnesota's Center for Infectious Disease Research and Policy (CIDRAP) websites.

Results

Internal Defense Against Bacteria:

As shown in Figure 1, the body's first line of defense is the skin; however, through an open wound, bacteria can easily infiltrate the defense. Once inside the body, the bacteria seek to reproduce quickly and spread; however, the body's second line of defense, the macrophages, is quick to respond to the new bodily threat. The macrophages have three main methods of destroying bacteria: autophagy, Reactive Oxygen Species (ROS), and apoptosis. Autophagy occurs when the bacterium is trapped inside a membrane called an autophagosome, which then joins a lysosome. The lysosome releases hydrolytic enzymes, which then digest the bacterium. ROS are created when a macrophage produces an enzyme that releases hydrogen peroxide, which kills harmful bacteria. Apoptosis occurs when a macrophage engulfs bacteria and self-destructs to limit bacterial replication and prevent further spread.[7]

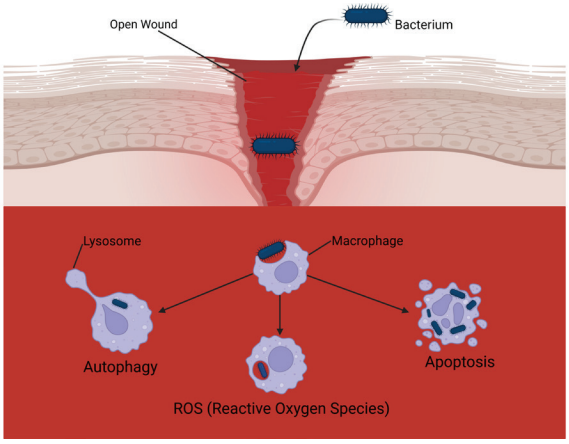

Figure 1: Innate defense mechanisms against bacteria. This figure shows different processes used by macrophages to kill bacteria, such as autophagy, ROS & apoptosis. Created by Pawar using Biorender.

Antibiotic Resistance:

Antibiotic resistance occurs when bacteria develop the ability to resist destruction from antibiotics. Bacteria develop resistance by genetic mutations or by acquiring resistant genes from other bacteria. Excessive antibacterial exposure or the use of lower doses of prescribed antibiotics helps resistant bacteria survive and multiply.

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a resistant strain of *S. aureus* that causes infection when open wounds or injuries are exposed to the bacteria. MRSA often arises in East Asian and South American countries due to excessive and unregulated antibiotic usage in those countries.[8] Approximately 1% of the general population carries MRSA. Untreated infections result in gangrene or deep abscesses in the skin, sometimes resulting in sepsis or death.[9] MRSA is a specific strain of *Staphylococcus aureus* that has developed resistance to many commonly used antibiotics. This bacterium acquires a mecA gene, which encodes an altered penicillin-binding protein (PBP2a) with reduced affinity for antibiotics such as methicillin. This allows bacteria to survive and grow even in the presence of antibiotics.[10]

Tuberculosis is a bacterial infection that occurs when the bacterium *Mycobacterium tuberculosis* enters the body through the nasal passages when one breathes in the droplets released by an infected person. The bacterium is then phagocytosed and destroyed by either T cells or lysosomal enzymes.[11] Mycobacteria develop drug resistance through mutations in different genes that help the bacteria survive anti-tuberculosis drugs. Phenotypic resistance is common in *M. tuberculosis* and results from changes in cell structure, which limit antibiotic access to their targets. Other resistance mechanisms seen in *M. tuberculosis* include efflux pumps and target pressure. Efflux pumps force the drug outside the bacterial cell, so it does not get killed. Target pressure occurs where *M. tuberculosis* develops mutations in genes that code for the antibiotic target site.[12]

Escherichia coli is an infectious bacterium that enters the human body after consumption of contaminated food or liquid, and it results in mild symptoms such as nausea, vomiting, watery diarrhea, or some toxin-producing strains can cause serious illness, such as kidney damage. This bacterium can spread from human to human under unhygienic conditions and through the fecal-oral transmission route.[13] Drug resistance mechanisms in *E. coli* include horizontal gene transfer, DNA integration, and porin modification. With horizontal gene transfer, *E. coli* can acquire resistant genes from other bacteria. DNA integration happens when the bacterium inserts a plasmid into its genetic code. Porin modification occurs when *E. coli* alters the pores in its cell membrane to control the flow of substances. This prevents the antibiotics from entering the bacterium, allowing it to survive and reproduce inside a host.[14]

Pseudomonas is a genus of bacteria known for causing severe infections. The most common species is *P. aeruginosa*, which is spread through contaminated water, soil, food, and medical devices such as ventilators and urinary catheters. According to a report by the Cleveland Clinic, it is one of the most common bacterial infections, making up to 25% of bacterial infections. *P. aeruginosa* is resistant to most antibiotics, as it can rapidly evolve to develop resistance in a specific strain. The drug resistance mechanisms in Pseudomonas include intrinsic resistance, mutations, and biofilms. Intrinsic resistance mechanisms include low outer-membrane permeability and drug efflux pumps. Additionally, *P. aeruginosa* can mutate, making it immune to some of the most effective antibiotics, such as penicillin and carbapenems. *P. aeruginosa* in the biofilms, commonly found in medical devices inside the body, leads to reduced antibiotic susceptibility and persistent infections.[15]

Antibiotics use leads to the elimination of susceptible bacteria. However, some bacteria survive through a variety of mechanisms of drug resistance, allowing them to survive, reproduce, and pass the mutations to their next generation. Over time, natural selection can cause resistant bacteria to become a dominant strain. Thus, the bacteria develop antibacterial resistance due to their existing genetic variations and evolution through natural selection. Understanding these drug resistance mechanisms is crucial in addressing the global challenge of antibiotic resistance.

Clostridium Difficile:

C. difficile is a gram-positive, spore-forming bacillus. In the environment, it survives in the spore form. It is spread via contact with the contaminated objects or the hands of healthcare workers. Once these spores are in the intestines, they convert into their functional, toxin-forming form. Antibiotic use is one of the major risk factors for *C. difficile* infection. Antibiotics can adversely affect the healthy gut flora, leading to an excess growth of *C. difficile*. Healthy infants and adult patients in hospitals or nursing homes may carry *C. difficile* in their gut flora, but it is often kept in check by other gut bacteria. Symptoms arise when there is overgrowth of *C. difficile*, and certain strains produce toxins. This can lead to mild symptoms like watery diarrhea and stomach cramping, while in severe cases, this infection can be life-threatening.[16]

Currently, antibiotics such as Vancomycin, Metronidazole, and Fidaxomicin are used to treat this infection. In some cases, these antibiotics are ineffective. Like other drug-resistant bacteria, *C. difficile* develops resistance by mechanisms such as genetic mutations, alterations in metabolic pathways, and biofilm formation.[17,18] Understanding drug resistance mechanisms of *C. difficile* and implementing those strategies to develop novel antibiotics, such as nano-antibiotics, would prove to be more beneficial in the prevention and treatment of this disease.[19]

Nano-carriers (Nano-antibiotics):

Nanotechnology is a branch of science that focuses on the development and usage of nanoparticles, or particles with a size between 1 nm and 100 nm. The nanoparticles are extensively utilized in biomedical sciences and engineering applications, primarily due to their high surface area, ease of surface modification and functionalization, and highly tunable structural and chemical properties. A proposed method to combat antibiotic resistance is the use of nano-carrier encapsulated antibiotics (also known as nano-antibiotics). Encapsulation of commonly used antibiotics with nanoparticles can serve several purposes. Nanoparticles can be bioengineered to deliver antibiotics to their target sites more efficiently. In addition, nanoparticles can protect the antibiotics from degradation by enzymes, which increases their half-life and bioavailability. If this can be properly executed, the effective dose of currently used antibiotics can be lowered. Additionally, metal nanoparticles such as gold, silver, copper, and iron are currently being used for their antibacterial properties.[20] As they act through multiple non-specific mechanisms, such as the generation of reactive oxygen species or membrane disruption, they have a broad spectrum of antibacterial activity. Incorporating nanoparticles into current infection management strategies can help reduce side effects associated with many antibiotics.[21,33]

As the concept of nano-antibiotics is still in its developmental stage, it is unclear if these nano-antibiotics would have any undesired short-term or long-term adverse effects. To avoid any adverse effects of nano-antibiotics, it is crucial to utilize a nano-carrier that has increased bioavailability and biodegradability, and is non-toxic to mammalian cells.[21,33]

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Table 1: Comparative analysis of various nanoparticles. The table displays various types of nanoparticles, their composition (organic/inorganic), shapes, and antibacterial activity.

Material	Organic/Inorganic	Shape	Bacteria
Silver nanoparticles	Inorganic	Spherical, Cubic, Nanorod	*Mycobacterium Tuberculosis, P. Aeruginosa, E. Coli*
Gold nanoparticles	Inorganic	Spherical, Cubic, Nanorod	*Yersinia Pestis, Salmonella spp.*
Zinc Oxide nanoparticles	Inorganic	Spherical, Cubic, Nanorod	*Mycobacterium Tuberculosis, MRSA, E. coli*
Copper nanoparticles	Inorganic	Spherical, Cubic, Nanorod	*L. Pneumophila*
Polymeric nanoparticles	Organic	Spherical, Cubic, Nanorod	*Methicillin-Resistant Staphylococcus Aureus, Mycobacterium Tuberculosis*
Liposome-based nanoparticle	Organic	Spherical, Multilamellar vesicles (MLV), Unilamellar vesicles (ULV)	*M. Avium Complex*
Solid lipid nanoparticles	Organic	Spherical, Polymeric core-shell	*Methicillin-Resistant Staphylococcus Aureus*
Carbon nanoparticles	Inorganic	Cylindrical nanotubes	*Mycobacterium Tuberculosis*
Chitosan nanoparticles	Organic	Cylindrical, spherical, irregular	*Brucella spp., Salmonella spp.*

Nanoparticles Classification:

As shown in Table 1, nanoparticles are a large and diverse group of compounds that vary in size, structure, and properties. They have different sizes and shapes: nanorods, nanospheres, nanotubes, nanowires, quantum dots, nano-shells, mesoporous silica, and nanotriangles, amongst many others. Nanomaterials have an extensive range of structures, such as fibers, fullerenes, hollow interiors, and reticular networks. The particles themselves have a wide variety of properties and molecular makeup. These nanoparticles differ in their properties, which include strength, elasticity, electrical conductivity, thermal conductivity, magnetism, and density. Metal nanoparticles include silver, gold, zinc oxide, and copper nanoparticles. Organic nanoparticles include polymeric, liposome-based, solid lipid-based, and chitosan.

Silver nanoparticles are one of the nanoparticles that have antibacterial properties. They exhibit the antibacterial effect by attaching to the bacterial cell surface, destroying proteins, and disrupting bacterial biofilms. Silver is a pure material because it has only one type of atom. Silver nanoparticles have been shown to have antibacterial effects on *M. tuberculosis, P. aeruginosa*, and *E. coli*.[21]

Gold nanoparticles can cause bacterial death by disrupting the bacterial respiratory chain, inhibiting the production of ATPase in bacteria, and decreasing the cell membrane potential. Gold is a pure substance and can halt the spread of *Yersinia pestis* and *Salmonella spp*.[22]

Zinc Oxide nanoparticles can be used to eliminate *M. tuberculosis*, MRSA, and *E. coli* by destroying and preventing bacterial biofilm formation, increasing the membrane permeability, elasticity, and degradation.[23]

Copper is a pure, inorganic metal and takes on almost all nanoparticle shapes. Copper nanoparticles have shown antibacterial activity against various bacteria such as *Staphylococcus aureus*, *Salmonella enterica*, *Campylobacter jejuni*, *Escherichia coli*, *Listeria monocytogenes*, and *L. pneumophila*. Copper nanoparticles exhibit antibacterial activity against *E. coli* by generating reactive oxygen species, lipid peroxidation, protein oxidation, and DNA degradation.[24]

Polymeric nanoparticles are organic nanoparticles that have a polymer matrix and a polymer shell.[25] These polymers are best used as a nanocarrier for antibiotics due to their variety of beneficial properties, such as biodegradability, versatility, and low toxicity. According to a study by Pandey *et al*., nebulized poly lactic-co-glycolic acid (PLGA) nanoparticles delivering anti-tuberculosis drugs in guinea pigs showed higher bioavailability than oral doses. This study demonstrated that using nanotechnology, it is possible to reduce the dosing frequency of the anti-tuberculosis drugs.[26]

Liposome-based nanoparticles are among the most widely used and effective nanocarriers because of their versatility. They can encapsulate most antibiotics, including hydrophilic and hydrophobic substances. A study by Mehta *et al*. showed that liposome encapsulation of a drug to treat *Mycobacterium Avium Complex* (MAC) infections in a mouse model reduced toxicity and improved therapeutic efficacy compared to the free drug.[27]

Solid lipid nanoparticles (SLNs) are colloidal carrier systems that have a solid biodegradable lipid matrix. They are organic, and their most common shape is spherical. They offer many advantages, such as improved stability of incorporated compounds and controlled release of drugs. Due to their biocompatibility, non-toxicity, and simple production procedures, SLNs are commonly used in biomedical applications. As nanocarriers, SLNs demonstrated enhanced antibacterial activity of drugs against resistant strains like MRSA and *P. aeruginosa*.[28]

Carbon nanoparticles, because of their chemical properties, are easily released into bacterial membranes. Due to their exceptional transportation skills, they are suitable to function as nanocarriers. Examples of carbon nanoparticles are quantum dots and 2D materials such as graphene and nanotubes. They are pure substances, meaning they consist of only carbon atoms. These nanoparticles can be used to treat *Mycobacterium tuberculosis* infection.[29]

Effectiveness of Nano-antibiotics in Treating S. aureus:

A study published in 2023 by Le et al. demonstrated that nanocarriers can be used to increase the effectiveness of antibiotics compared to conventional antibiotics. The bacteria tested in this study were *Staphylococcus aureus*. The researchers tested two commonly used antibiotics to treat *S. aureus*: ciprofloxacin and levofloxacin. They encapsulated these antibiotics with polymer-based nanoparticles called poly lactic-co-glycolic acid (PLGA). In addition, the researchers modified the antibiotic surfaces by altering the antibodies complementary to the bacterium. Due to these modifications, the researchers demonstrated that the antibiotics were more efficient in identifying and eradicating bacteria. They observed bacterial growth using microscopes and fluorescent dyes that made the bacterial cells easier to visualize. After testing conventional antibiotics, targeted nano-antibiotics, and non-targeted nano-antibiotics, the researchers found that targeted nano-an-

tibiotics functioned better at killing *S. aureus* than conventional antibiotics. Non-targeted nano-antibiotics had slightly less efficacy compared to conventional antibiotics. However, the targeted nano-antibiotics were the most effective and efficient in killing *S. aureus*. Non-targeted nano-antibiotics and conventional antibiotics decreased the number of *S. aureus* colonies by around 10 times. Astonishingly, targeted nano-antibiotics decreased the number of colonies nearly 100-fold.[30]

Effectiveness of Lipid Nanoparticles & Chitosan as Nanocarriers:

Bacterial biofilms are a group of microorganisms that are ingrained into a substance called Extracellular Polymeric Substance (EPS), which is made of lipids, proteins, polysaccharides, and nucleic acids. Bacterial biofilms can stick to cell surfaces and lead to antimicrobial resistance because few antibiotics can penetrate through the biofilm. The bacterial biofilms are developed over time in five stages that include: attachment, colonization, development, maturation, and dispersal. There are several approaches currently being researched to inhibit the growth of bacterial biofilms.

A study published in 2024 by Ahsan *et al*. discussed the use of lipid nanocarriers in the treatment of bacterial biofilms. A combination of antibiotics with antimicrobial adjuvants such as EPS degrading enzymes or quorum-sensing inhibitors (QSI) can be encapsulated by lipid nanoparticles. EPS degrading enzymes can be used to eradicate biofilms, and QSI are the agents that block bacterial communication, halting the development of biofilm. Lipid nanocarriers are promising nanocarriers for this strategy due to their greater bioavailability, drug protection from enzyme degradation, and targeted drug delivery. This strategy can improve the effectiveness of antibiotics and decrease antimicrobial resistance.[31]

Chitosan is a naturally occurring amino polysaccharide that has extraordinary biocompatibility and biodegradability. For decades, Chitosan has been used in drug delivery systems and in different applications in various medical fields such as orthopedics, ophthalmology, and surgery. Chitosan nanocomposites contain chitosan polymers that are less than 100 nm. Thus, Chitosan nanocomposites are considered a promising and safe nanocarrier for biomedical applications.[32]

Discussion

As antibiotics have been used for decades, their mechanism of action, pharmacokinetics, and pharmacodynamics are well-studied. The FDA approves, on average, one to two antibiotics every year. However, resistant strains to these antibiotics appear more rapidly. Therefore, it is of vital importance to develop novel alternatives to traditional antibiotics. The nanotechnology industry has become a significant part of this endeavor by utilizing nanoparticles with antibiotic properties or by encapsulating antibiotics with nanoparticles. Despite the demonstrated antibacterial activity of some nanoparticles, such as silver nanoparticles, the precise molecular mechanism by which these nanoparticles exhibit the antibacterial effect is partially understood.

Currently, nanomaterials are used in targeted drug delivery to cancer patients. In these treatments, nanoparticles loaded with chemotherapy drugs are coated with ligands that bind to specific receptors on cancer cells. Cancer cells identify these ligands as their own and internalize the nanoparticles, enabling chemotherapy drugs to be delivered directly to cancer cells while sparing healthy tissue. This targeted approach improves effectiveness and reduces side effects compared to traditional cancer treatments. Similar strategies could be adapted for more precise antibiotic delivery. Currently used nanoparticles lack specificity for the bacteria. Therefore, developing nanocarriers with specific targeting molecules for pathogenic bacteria is very important. Since nanoparticles cannot distinguish between probiotic and pathogenic bacteria, dysbacteriosis may occur in the human body.

Utilizing targeted antibiotic delivery using nanoparticles as carriers would limit the antibiotic's exposure to non-targeted cells, thus decreasing their adverse effects and improving patient outcomes. Some nanoparticles, such as silver nanoparticles, are cytotoxic, which limits their *in vivo* applications. Managing this cytotoxic effect is essential to ensure the safety of nanoparticle-based treatments. Therefore, selecting or designing nanocarrier systems that maintain strong antibacterial properties while minimizing harm to human cells is a critical aspect of developing effective and safe nano-antibiotics. Currently, the best nanocarrier nanoparticle coatings are Solid Lipid Nanoparticles (SLNs), which are organic compounds with limited cytotoxicity and have a similar antibacterial effect to other inorganic nanoparticles.

Nano-antibiotics would have traditional antibiotics encapsulated with nanoparticles. The use of conventional antibiotics in the nanocarrier's core would deliver antibiotics to their target, allowing them to accomplish their goal. These nano-antibiotics combine the unique advantages of nanomaterials, such as enhanced bioactivity and reduced antimicrobial resistance, with the well-established mechanisms of traditional antibiotics, making them a promising next-generation antimicrobial treatment option.[33] In summary, advancing nano-antibiotics will require targeted research into their precise antibacterial mechanisms, pathogen-specific selectivity, and long-term biosafety.

Conclusion

Antibiotic resistance remains a major global threat to humanity, as antibiotics once considered dependable continue to be ineffective. Moreover, inappropriate use of antibiotics can lead to severe side effects and secondary infections, such as *C. difficile*, emphasizing the urgent need for safer and more efficient drug delivery systems.

Nano-antibiotics offer a promising solution to address this critical issue by encapsulating the conventional antibiotics within biodegradable, non-toxic nanocarriers. This approach can enhance targeted drug delivery, increase drug bioavailability, and minimize systemic toxicity. Additionally, nano-antibiotics demonstrate significant potential in treating the biofilm-associated resistance by achieving controlled and sustained drug release at the site of infection. Future research

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should focus on understanding the long-term safety, pharmacokinetics, and potential cytotoxicity of these nanomaterials.

Ultimately, integration of nanotechnology into antimicrobial therapy could positively impact the existing model of infectious disease treatment. Through continued interdisciplinary research, nanotechnology truly has the potential to aid scientists in the fight against antibiotic resistance, enhance antibiotic efficacy, and contribute to the development of next-generation antibacterial therapies.

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