



SILVER NANOCOMPOSITES: A GLIMPSE INTO THEIR GAME-CHANGING ROLES IN ANTIBACTERIAL THERAPY

GÜMÜŞ NANOKOMPOZİTLER: ANTİBAKTERİYEL TERAPİDEKİ OYUN DEĞİŞTİRİCİ ROLLERİNE BİR BAKIŞ

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ABSTRACT

Objective: The application of nanocomposites in biomedicine is a promising approach that scientists have discovered to eradicate infection-causing microorganisms properly and safely. Silver nanocomposites (AgNCs) can be recognized as hopeful antibacterial prospects that can fight both in vivo and in vitro infection-causing bacteria. The purpose of this review is to identify the variables that influence the antibacterial effect of AgNCs, given the pressing need for new, effective antibacterial agents.

Result and Discussion: In the literature, many reports indicate the capacity of AgNCs to combat both gram-positive and gram-negative bacteriomers, including those that are resistant to multiple drugs. This capacity is due to the multiple simultaneous modes of AgNCs action. This capacity also results in a synergistic impact on bacteria when mutually applied with natural or synthetic antibacterial medications. Because of their unique properties, AgNCs can be effectively used to manage or prevent infections in a variety of medical and healthcare products. The study focuses on the synthetic methodologies and antibacterial mechanisms of AgNCs. Furthermore, factors influencing the action of AgNCs against bacteriomers as well as the advantages of combining AgNCs with antibiotics to create novel antibacterial combinations were covered. The authors wanted to make it possible to reduce the dose required and prevent unfavorable off-target effects associated with both by providing access to the reviewed data.

Keywords: Antibacterial activity, antibiotic, silver nanocomposites, synergistic effect

ÖZ

Amaç: Nanokompozitlerin biyomedikal alanda uygulanması, bilim insanlarının enfeksiyona neden olan mikroorganizmaları uygun ve güvenli bir şekilde ortadan kaldırmak için keşfettiği umut verici bir yaklaşımdır. Gümüş nanokompozitler (AgNC'ler), hem in vivo hem de in vitro enfeksiyona neden olan bakterilerle savaşılabilen umut verici antibakteriyel olasılıklar olarak kabul edilebilir. Bu incelemenin amacı, yeni ve etkili antibakteriyel ajanlara olan acil ihtiyaç göz önüne alındığında, AgNC'lerin antibakteriyel etkisini etkileyen değişkenleri belirlemektir.

Sonuç ve Tartışma: Literatürde, birçok rapor, AgNC'lerin çoklu ilaçlara dirençli olanlar da dahil olmak üzere hem gram pozitif hem de gram negatif bakteriyomerlerle savaşma kapasitesini göstermektedir. Bu kapasite, AgNC'lerin birden fazla eşzamanlı etki modundan kaynaklanmaktadır. Bu kapasite, doğal veya sentetik antibakteriyel ilaçlarla birlikte uygulandığında bakteriler üzerinde sinerjik bir etkiyle de sonuçlanmaktadır. Benzersiz özellikleri nedeniyle, AgNC'ler çeşitli tıbbi ve

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sağlık ürünlerindeki enfeksiyonları yönetmek veya önlemek için etkili bir şekilde kullanılabilir. Çalışma, AgNC'lerin sentetik metodolojilerine ve antibakteriyel mekanizmalarına odaklanmaktadır. Ayrıca, AgNC'lerin bakteriyomere karşı etkisini etkileyen faktörler ve AgNC'leri antibiyotiklerle birleştirerek yeni antibakteriyel kombinasyonlar oluşturma avantajları ele alınmıştır. Yazarlar, incelenen verilere erişim sağlayarak gereken dozu azaltmayı ve her ikisiyle ilişkili olumsuz hedef dışı etkileri önlemeyi mümkün kılmak istemişlerdir.

Anahtar Kelimeler: Antibakteriyel aktivite, antibiyotik, gümüş nanokompozitler, sinerjik etki

INTRODUCTION

Bacteria quickly create antibiotic resistance strategies because of their enormous populations and high growth rates. This may happen when a portion of the bacterial population is exposed to antibiotics continuously at low doses [1]. However, misuse and abuse of antibiotics have been considered one of the main reasons for the increase in infections caused by antibiotic-resistant bacteria in recent years [2]. As infections brought on by multi-resistant microorganisms continue to spread and claim lives all over the world, research into the creation of new antibiotics is currently a challenging process that takes years to complete and involves extensive time and resource consumption [3,4].

Nanotechnology is a field that works with substances providing at least one dimension varying between 1 and 100 nm with the goal of obtaining novel particles and materials. Nanocomposites are quite distinct from macrocomposites because the former composite type has special, superior, and indispensable characteristics compared to the latter type [5]. The distinct nanoscale structure of nanocomposites confers exceptional properties, setting them apart from macrocomposites. Nanocomposites have a significantly better total area-to-volume ratio than macrocomposites because they contain nanoparticles with at least one dimension in the nanometer range. The matrix and filler's interfacial contacts are strengthened as a result, improving electrical conductivity, toughness, and heat stability. In the medical, automotive, and aerospace industries, for example, nanocomposites are essential due to their improved barrier qualities, decreased weight, and increased flame retardancy [6,7]. Furthermore, they can be molecularly tuned to achieve multifunctionality, something that macrocomposites cannot do [8]. Nanocomposites are water-insoluble particles whose size is less than 100 nanometers, which makes them have a greater surface-to-volume ratio (per unit mass), which gives them more surface area for antibacterial action and enables them to interact more closely with the bacterial membrane. Historically, antimicrobial agents have been created using silver in all of its forms, either alone or in conjunction with other methods [9]. AgNCs improved antibacterial capacity at the nanoscale has proven particularly useful in the medical care and health services fields, where the integration of AgNCs into many different products—such as surgical instruments, cosmetics, dental products, and dressings—has been researched [10]. By combining silver, either as silver nitrate or silver sulfadiazine, in food containers in order to stop contamination, burn and ulcer treatment creams, and various industrial applications, researchers have explored how to best utilize this metal's ability to limit bacterial growth [11].

Since ancient times, the biological technique has used microbes or medicinal herbs to create nanocomposites [12]. AgNCs have demonstrated antimicrobial effectiveness against a range of virulent and infectious pathogens. This is due to their strong antimicrobial efficacy against a wide range of bacteria, viruses, and fungi, as well as their broad-spectrum antimicrobial properties [13]. AgNCs are being used increasingly in consumer products, such as nutritional supplements, apparel, and packaging, due to their antibacterial characteristics against antibiotic-resistant microorganisms [14]. The prospect for AgNCs to be more hazardous than equal quantities of dissolved silver has been demonstrated in laboratory tests with plants and microorganisms [15]. Due to its distinct qualities and potential uses, nanocomposite manufacturing has attracted a lot of interest lately. Whether they are simple or composite, nanocomposites have distinctive features and are increasingly being employed to create novel nanodevices for a variety of physical, biological, biomedical, and therapeutic purposes [16]. As a result, there may be an urgent need to find new medications to replace those that are now in use. Most nanocomposites have special qualities that are useful in many biotechnology applications, resulting in their use in the creation of incredibly efficient diagnostics and therapeutic tools [17].

Because of AgNCs' distinctive characteristics, which include biomedical traits like antibacterial, delivery of medication, cancer-fighting, and immune-modulating activities, scientists are interested in

using AgNCs in nanotechnology applications [18]. Several scientific domains were significantly impacted by the invention of AgNCs' synthesis. The nanocomposites have drawn a lot of attention because of the significant demand and expenditure in associated research. The market for AgNCs has been expanding steadily over the past fifteen years, and production of over five hundred tons of nanocomposites annually is estimated to be needed to meet the demands of various industries [19]. The investigation of the biological function and safety of AgNCs, as well as the clarification of their precise modes of action in microbial and human cells, have become pressing issues [20]. These are due to the global expansion of the nanocomposite market and the availability of goods containing them. This brief overview covers the use of AgNCs in medicine to inhibit the growth of or kill bacteriophages, which can be an alternative to or with antibiotics. The headings and subheadings of the subjects discussed in this paper are graphically represented in Figure 1.

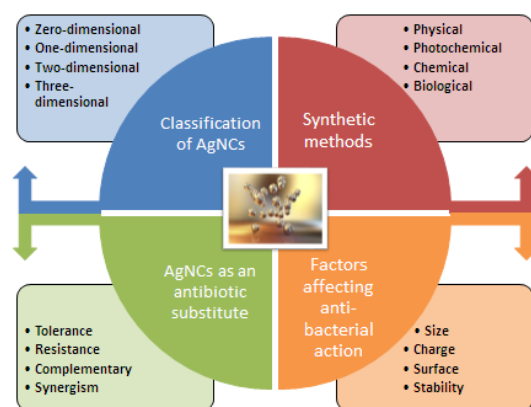


Figure 1. Graphical representation of the main subjects investigated in this review study

Classification of AgNCs

AgNCs can be roughly categorized into four distinct categories [19]: Zero-dimensional nanocomposites (Figure 2a), such as an aggregation or nanoshell, are measured in every dimension on the nanoscale. One-dimensional nanocomposites (Figure 2b) with a single layer that range in size from 1 to 100 nm. They are employed in many different fields, including solar cells, and they support a wide range of technological applications, including fiber-optic systems, natural sensors, and storage devices. Two-dimensional nanocomposites (Figure 2c), such as carbon nanotubes, and three-dimensional nanocomposites (Figure 2d), like quantum dots.

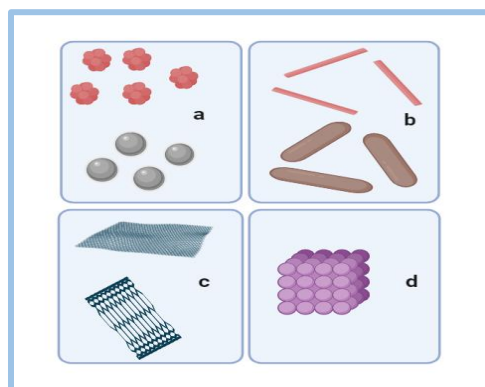


Figure 2. Various currently available categories of AgNCs

Methodologies for Creating AgNCs

The need for environmentally friendly, non-toxic nanocomposite production techniques that reduce the usage of hazardous chemicals as byproducts has spurred interest in biomedicine fields [21]. AgNCs have been considered a popular ingredient in many health products due to their exceptional ability to combat infectious disorders and stop the growth of bacteria, mold, and germs. They have unique chemical-, optical-, electrical-, magnetic-, and mechanical-based properties [18,22]. The main methodologies found in the literature for creating AgNCs are four, and they are explained below.

Physical Methodology

This method involves creating metal nanocomposites or wires through evaporation or intensification, which can be accomplished by keeping the furnace tube at the atmosphere's pressure. In the furnace, the materials inside a fixed vessel vaporize into the carrier gas. The vaporization process and intensification techniques were used to create nanosized particles of several materials, such as copper, silver, zinc, tin, and lead, as well as fullerene [23]. As a result, producing nanocomposites in a furnace has several drawbacks since the cylinder-shaped material requires a lot of energy, takes up a lot of space, raises the ambient temperature, and takes a while to achieve thermal consistency [24].

A unique cylinder-based furnace must heat for ten minutes to reach a steady temperature, using many kilowatts of energy. Moreover, laser ablation of the whole substance in a solution has been used to create AgNCs [19]. The advantage of the laser technique over the other approaches is that pure colloids may be manufactured and there is no need for a chemical reagent in solution, making it more beneficial in a variety of applications [25]. In general, AgNCs with full-size circulation are produced by physical methodology with the assistance of physically generated energy [26].

This type of method may effectively produce AgNCs in the form of ash while enabling the production of large quantities of product with a single methodology. Physical methodology can produce a huge amount of high-purity AgNCs. It produces stable AgNCs by synthesizing nanocomposites from solid or aerosolized metallic silver down to the nanoscale [27]. This group includes physical techniques including sputtering, laser ablation, and grinding balls. Unfortunately, high pressure and temperature conditions, costly instrumentation, and significant energy requirements are typically associated with these techniques [25,28].

Photochemical Methodology

Both Huang and Yang created AgNCs via the photoreduction of silver nitrate layers. This method is based on innocuous soil suspensions that serve as stabilizing oxidants to prevent particle aggregation. AgNCs were irradiated and split according to their distribution ratio until they reached a consistent size distribution ratio and absolute diameter. Nevertheless, there were some prerequisites, such as an expensive setup and an experimental setting [29].

Chemical Methodology

All options considered, the chemical methodology is the most effective, practical, and manageable. This process, which can be done relatively cheaply and with great productivity, is widely employed to produce AgNCs by chemical reduction. The chemical approaches of AgNCs in real solution usually involve three steps: Capping oxidizing agents, reducers, and metal-based precursors [30]. In addition, the utilization of capping agents in this method enables the regulation of metal-based nanocomposite growth, which is necessary to obtain tiny nanocomposite particle with a spherical form. To prepare a colloidal solution, the silver-natured salt reduction has two phases of development and nucleation. The shape of the nanocomposites depends on these two processes [29]. Nonetheless, the synthesis of particles with the same size and development rate is the prerequisite for the manufacture of single dispersed nanocomposites with regular sizes. By controlling the reaction utilizing various restrictions, such as precursors, pH, temperature, reducing substance, and capping material, the ensuing formation of primary nuclei may be detected [31].

Biological (Green Chemical) Methodology

The term "green chemistry" is another name for the biosynthetic technique that uses reducing agents such as biological microorganisms, polysaccharides, extracts from plants, bacteria, or fungi [32]. It is commonly known that bacteria can create inorganic substances both inside and outside of their cells. According to Yaqoob et al. (2019), they thus serve as more viable biofactories for the production of nanocomposites such as gold, copper, silver, etc. [19]. One of the acknowledged particles having biotic properties is the creation of AgNCs. Silver and gold nanocomposites can be created by Vilchis-Nestor et al. (2008) using an aqueous *Camellia sinensis* extract under ambient circumstances. This extract was employed as an agent for stabilization and reduction [33]. However, Kalishwaralal et al. (2008) also mentioned that AgNCs were produced by reducing their ions with *Bacillus licheniformis* supernatant [34]. This approach offers greater benefits than the others because non-pathogenic bacteria were employed, and AgNCs are incredibly stable. This method is both stable in terms of the environment and economical. However, the large-scale production of nanocomposites or wires via a biological technique is challenging [35]. Table 1 demonstrates the different approaches together with their methods and useful aspects.

Table 1. The various methodologies together with their techniques and practical qualities

Creating methodologies	Properties	Techniques	Basic requirements
Physical methodology	Produce homogeneous colloids solution in large quantities in a single operation.	Methods include chemical etching, ablation with lasers, and ball milling	Sophisticated, pricey equipment, and High atmospheric pressure, enormous energy
Photochemical methodology	Extremely sophisticated instruments, exact diameter, consistent size, and mean distribution ratio acquired	Photodissipation or photodegradation	Extended periods of time and high-priced equipment in an experimental setting
Chemical methodology	Successfully inexpensive, and easy to use a technique that produced spherical-shaped particles	Electrochemical technique, reduction of chemicals	Metal precursors and capping and reducing agents
Biological (green chemical) methodology	Cheap, stable in the environment, and intricate to operate	Technique mediated by plants algae-mediated approach, bacteria -and fungus-mediated approach	Algae, fungus, and bacteria that are Non-pathogenic, reducing agent

General Aspects of AgNCs Activity Against Pathogenic Bacteriomers

Since antibiotic-resistant bacterial infections are a major worldwide health concern, AgNCs present a great substitute. This is because they can be used to stop infections brought on by these bacteriomers, clean medical equipment, and even treat infections as they occur [36]. This substitution has received a lot of attention recently as an alternative to antibiotics, with the goal of creating new bactericidal items for infection therapies that take advantage of what is known about their effectiveness. Nanotechnology, the application of materials with atomic- or molecular-scale dimensions, has grown in popularity for medical uses and is highly sought-after as a method of eradicating or suppressing the activity of several pathogens [37]. Some naturally occurring antibacterial materials, like silver, exhibit enhanced antibacterial properties as they get smaller within the nanometer order (because of an increase in the surface-to-volume ratio for a given mass) [38]. However, different antibacterial mechanisms may be related to the physical composition of the nanocomposites and how they interact with and introduce

pathogens. To obtain nanocomposites with antibacterial properties, the shape and size of the nanocomposites are among the most important characteristics that are supposed to be present in order to achieve this effect. It should be 3–100 nanometers in size, but the shape varies: spherical, cubic, triangular, pentagonal, hexagonal, and nanowire [39].

All shapes were able to connect and eventually cause destruction of the bacterial cell's membrane, according to observations of the membrane structure. The most facets, however, are found in the truncated triangular shape, which promotes bacterial contact and increases surface binding, cell absorption, and bacterial killing [13]. AgNCs have the potential to be antibiotics because of their diverse modes of action, which allow them to kill different kinds of bacteria by attacking them simultaneously in several structures [40]. The antibacterial activity of AgNCs (5–9 nm) is inversely correlated with their size. Also, this activity has significantly increased, especially below 10 nm, according to Shim et al. [14]. Reactive oxygen species accumulation and making the bacterial membrane more invaded are both correlated with the smaller size of the nanocomposites used [39].

Different methodologies were used for checking the antibacterial effect of AgNCs; however, the disk and well diffusion approaches are the most common [41]. Minimum inhibitory and minimum bactericidal concentrations (MIC and MBC), respectively, were also used. MIC detects the concentration of AgNCs that can inhibit the visible growth of the bacterial population using the broth dilution method. To determine MBC, a fixed AgNCs concentration above the value of the MIC is added to nutritional media. This is in addition to increasing microbial inoculum, and bacterial growth is observed using UV-V spectroscopy or a plate analyzer for changes in the samples' optical densities [42]. The bacteriomer's shape and structure were also monitored before and after exposure to AgNCs using transmission electron microscopy and scan electron microscopy [43]. Combining AgNCs with antibiotics has been shown to boost their antibacterial efficacy, particularly against drug-resistant bacteriomers. This combination has been proposed as a possible way to overcome medication resistance in bacteria in the recent past. It was suggested that coupling different antibacterial agents would increase their mutual antibacterial effectiveness [44,45].

Table 2. Some bacteriomers that reported to be inhibited by AgNCs

Bacteriomer	Reference	Bacteriomer	Reference
Gram positive		Gram negative	
<i>Lactobacillus fermentum</i>	[43]	<i>E. coli</i>	[49]
<i>Streptomyces sp.</i>	[50]	<i>Escherichia fergusonii</i>	[51]
<i>Streptococcus mutans</i>	[51]	<i>Vibrio cholera</i>	[52]
<i>Bacillus cereus</i>	[51]	<i>Ureibacillus thermo sphaerius</i>	[53]
<i>Bacillus anthracis</i>	[46]	<i>Pseudomonas aeruginosa</i>	[54]
<i>Brevibacterium casei</i>	[55]	<i>Salmonella typhimurium</i>	[55]
<i>Enterococcus faecalis</i>	[5]	<i>Acinetobacter baumannii</i>	[56]
<i>Staphylococcus aureus</i>	[49]	<i>Shigella sp</i>	[57]
<i>Staphylococcus epidermidis</i>	[5]	<i>Enterobacter aerogenes</i>	[58]
<i>Bacillus licheniromis</i>	[40]	<i>Klebsiella pneumoniae</i>	[59]
<i>Listeria monocytogenes</i>	[5]	<i>Proteus mirabilis</i>	[46]

Against a variety of bacterial species, both gram-positive and gram-negative, AgNCs have demonstrated strong antibacterial activity [46]. The bacteriomers that are reportedly influenced by the use of AgNCs are listed in Table 2. The available experimental data supports a variety of ways that take into account the physical characteristics of AgNCs, such as their size and surface. These ways enable them to interact with intracellular components or even pass through membranes and cell walls. When exposed to the same quantity of silver ions, gram-positive (e.g., *Staphylococcus aureus*) and gram-negative (e.g., *E. coli*) bacteriomers have been shown to exhibit DNA condensation, cell membrane division from the bacterium wall, and cell wall destruction. Additionally, each species of bacterial

cytoplasm included silver ions. These results shed more light on the function of metal ions in silver's antibacterial properties [47]. All forms of AgNCs showed dose-dependent suppression of bacterial activity. It's possible that the creation of nanoplates added a positive charge to the outer layer of the small particles, enhancing the electrical interactions between particles and bacteriomers. In summary, the antibacterial activities of AgNCs were due to the influence of silver ions on DNA replication, respiration routes, and the cellular membrane's integrity [48].

Mechanisms of AgNCs Antibacterial Potential

Three mechanistic processes that have been identified as working together or independently to explain how AgNCs inhibit bacteriomers are the main ones supported by the literature [60]. According to the first mechanism, AgNCs function at the plasma membrane level because they can pass through the exterior membrane and accumulate in the interior membrane. The adherence of AgNCs to the cell causes it to become unstable and damaged, enhancing the permeability, causing cellular content to leak out, and ultimately causing the cell to die. Additionally, it has been demonstrated that AgNCs can bind with sulfur-containing proteins in bacterial cell walls, which could result in structural damage and cell wall rupture [61]. According to the second mechanism, AgNCs can enter cells and change their composition and permeability by breaking through the membrane of the cell. It has been proposed that the distinct characteristics of AgNCs will enable them to communicate with intracellular components, such as DNA and proteins, in order to change their structure and function by phosphorous or sulfur moieties. In a comparable way, AgNCs may modify the respiratory pathway of the interior membrane by engaging with the SH residues in the corresponding enzymes [62]. These events trigger the apoptotic process, generate harmful free radicals, and disrupt intracellular machinery. Simultaneously with the first two mechanisms, a third process is proposed: the AgNCs discharge silver ions. These positively charged ions may communicate with biological parts, altering pathways of metabolism, membranes, and even nucleic acids due to their size and charge [63]. Figure 3 depicts these three fundamental processes proposed for the antibacterial action of AgNCs.

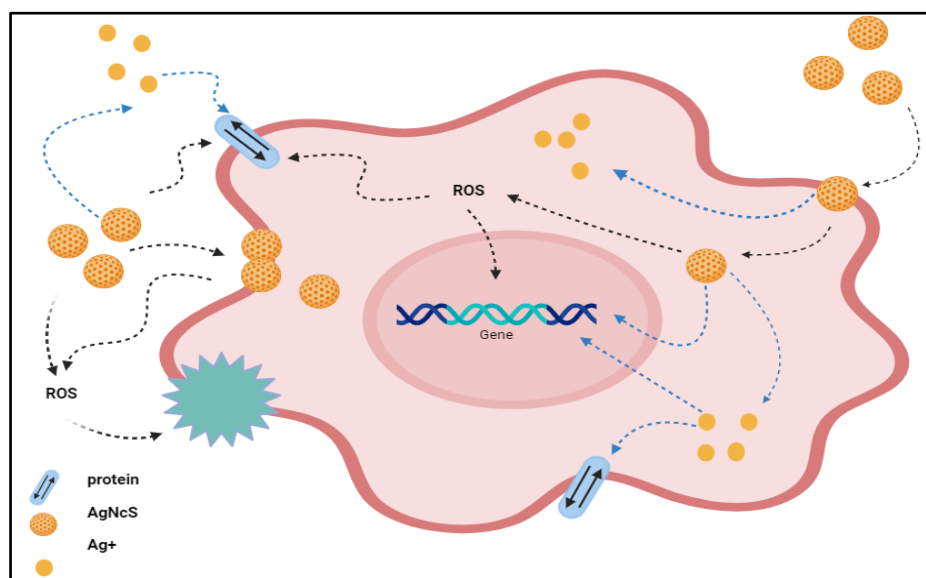


Figure 3. A diagram illustrating the pathways linked to AgNCs' antibacterial properties

Numerous renowned tactics that bacteriomers have evolved to make antibiotics useless. These tactics include obtaining drug-fighting genes from other species, growing biofilms, erecting obstacles to prevent antibiotics from penetrating, altering the drug's target, and removing the antibiotic from the intracellular medium by employing out-pump processes [64]. The fundamental mechanisms of resistance to antibiotics in bacteriomers involve drug inactivation, efflux pumps, entry barriers, and

structural alterations in response to drug targets. It also emphasizes the anti-bacterial mechanisms of AgNCs, including DNA damage, membrane accumulation, electron transport chain interference, efflux pump modification, and structural alterations. The foundation for these tactics is shown in Figure 4, which also shows that AgNCs may still affect bacteriometers regardless of drug-fighting mechanisms. AgNCs' antibacterial actions allow them to be used in combination with antibiotics or other lab-generated antibacterials as a supplement to their established capacity to inhibit biofilm growth [65].

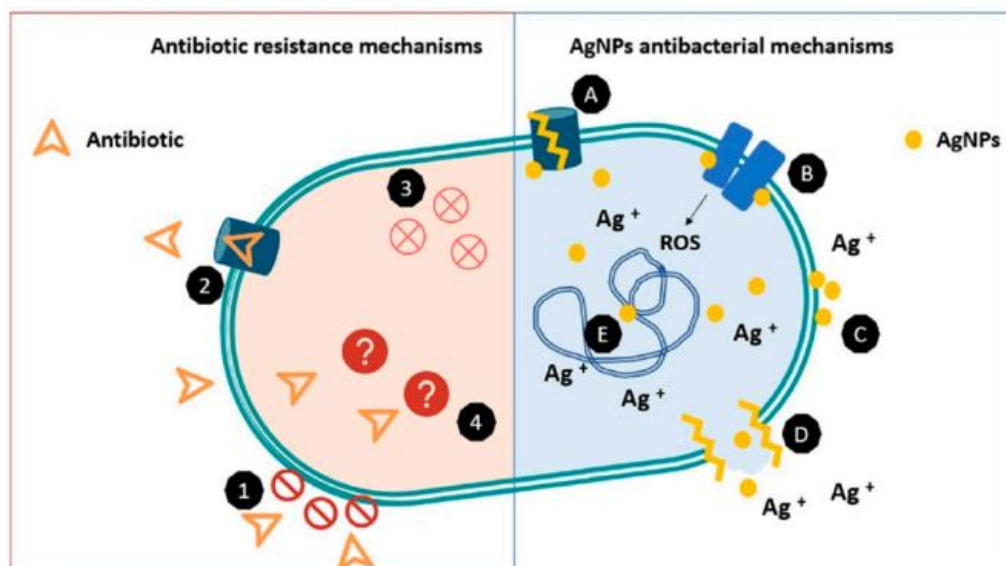


Figure 4. Comparison between the antibacterial mechanistic process of AgNCs and the resistance mechanisms of bacteriometers [9]. The following are the antibiotic- or synthetic antibacterial-resisting mechanisms: (1) entry hurdles; (2) outflow motors; (3) drug inactivation; and (4) structural modifications to drug targets (denoted as "?") that impede drug recognition. Conversely, AgNCs' antibacterial mechanisms involve the following: (A) modification of efflux pumps; (B) interference with electron transport chains and membrane proteins; (C) accumulation in the membrane that affects penetration; (D) change of the membrane structure and leakage of bacteriometers intracellular content; and (E) interaction and damage to DNA

The development of AgNCs was a logical and convincing step because silver has historically been used as an antibacterial agent. In the literature, there are many reports on how AgNCs work to kill bacteria [66]. The first thing that was believed to be impacted was membrane permeability due to the abundance of nanocomposites found inside the bacterium. The interaction of AgNCs with the bacterial membrane and proteins, especially those with sulfur, as well as DNA containing phosphorus, prevents cell division and results in cellular death [67]. The existence of biocidal ionized silver emitted from nanocomposite surfaces has also been confirmed by many published papers. Bacteria's DNA aggregation defense systems shield them from a hazardous environment when exposed to ionic silver, but this impairs the bacteria's capacity for replication. Ionic silver and its nanocomposites elicit different reactions, yet both are necessary to fully understand the antibacterial activity of AgNCs.

It is noteworthy that the use of AgNCs coupled with antibiotics for the medical treatment of bacterial infections has not been linked in the literature to the emergence of resistance. This finding may be connected to the mechanisms that govern the action of both of these agents [68,69]. AgNCs attack multiple cellular structures, whereas antibiotics only target one specific target in bacteriometers. AgNCs attack multiple cellular structures, whereas antibiotics only target one specific target in bacterial cells. As a result, when an antibiotic-AgNCs combination is used together, nanocomposites interact, act, and accumulate in bacterial walls and membranes. Since they can change and dissolve cellular barriers and membrane proteins, AgNCs allow antibiotics to work at the intracellular level. So, AgNCs are increasing

the concentration of antibiotics, debilitating bacteriomers, and even avoiding already-existing mechanisms of resistance [9].

Variables Impacting AgNCs Activity Against Bacteriomers

It has been shown through experiments that AgNCs' characteristics affect their antibacterial activity [60]. The ways in which AgNCs interact with bacteriomers are connected to how these properties affect their antibacterial potential. It has been found that the characteristics that increase antibacterial activity are also those that encourage interactions between bacteriomers and AgNCs. Accordingly, it is possible to manipulate and fabricate AgNCs in order to achieve the desired goals. This results in the emergence of an antimicrobial substance that can be prepared with optimized characteristics. In addition to the molecular components of AgNCs antibacterial action being clarified, it has been shown that many variables affect their antibacterial potential, which are listed below [9,44].

Composite Size

It was discovered that AgNCs prevented the development of gram-negative bacteriomers, especially *E. coli*, *Vibrio cholerae*, *Salmonella typhi*, and *Pseudomonas aeruginosa*, on agar plates with an average size of 21 nm and concentrations at or above 75 g/ml [70]. Lu et al. conducted a study to explore the effect of size on the antibacterial activity of AgNCs against the bacteriomers responsible for caries and periodontal diseases [71]. AgNCs were created in various sizes, and their antibacterial efficacy was assessed. It was discovered that smaller AgNCs had superior antibacterial activity compared to larger ones, with lower MIC limits [71]. In a subsequent study, the same agents and overall methodology were used to create AgNCs of various sizes. The variants are the pH levels and ratios of the stabilizing and reducing agents in the reactions that were altered. Then, against both gram-positive and gram-negative bacteriomers, the bacterial potential of AgNCs sizing 5-100 nm was assessed. The obtained MIC varied between small and large particle sizes, indicating lower concentrations in small particles relative to larger ones [72]. The increased surface area of the smaller nanocomposites, which is available for direct interaction with the bacterial cell, is thought to be the reason for the size dependence of the antibacterial activity, as demonstrated by the MIC data [73].

In further research, the efficacy of five different AgNCs to inhibit *Pseudomonas aeruginosa* and *Escherichia coli* was evaluated after they were created via chemical reduction. The results of the investigation showed that the AgNCs with the biggest diameter (30 to 200 nm) displayed the lowest activity with tiny inhibition halos. On the other hand, the smallest nanocomposites (15 to 50 nm) produced the most activity, with an inhibitory growth halo greater than that [74]. A more recent study assessed the antibacterial efficacy of laser-generated AgNCs in different sizes against *E. coli*. Antibacterial activity and AgNCs' size were similarly shown to be inversely correlated in this case; the most potent antibacterial activity was displayed by AgNCs with an average size of 19 nm. In this instance, the researchers demonstrated that smaller AgNCs would produce more reactive oxygen species and, as a result, be more potent against *Escherichia coli* [75].

Composite Charge and Surface

Regarding the charge's impact, it has been shown that particles with a positive charge exhibit stronger antibacterial activity [64]. Abbaszadegan et al. [76], stated that the electrostatic interaction between positively charged AgNCs and negatively charged bacteriomers is what drives AgNCs' antibacterial activity. So, the key factors are the charge of the AgNCs and that of microorganisms. Remarkably, the rate at which silver ions are released from the AgNCs is correlated with both size and surface features. While the size of the particles influences their contact area and interaction with the medium, the surface and charge of the AgNCs dictate their stability [77]. Accordingly, it has been noted that smaller AgNCs dissolve more quickly in various environments and release silver ions throughout the process, which may have a significant impact on their antibacterial activity [78].

Composite Stability

The AgNCs' stability is a crucial component influencing their ultimate antibacterial activity once the impact of size and charge on their survivability has been elucidated. The low stability of the

generated AgNCs will cause them to aggregate and form larger particles, and research has shown that larger AgNCs have less antibacterial action. The electrical charge and the covering are the main factors influencing AgNC's stability. Both the coating agent employed and the synthesis methodology may specify this value [79].

AgNCs as Antibiotic Substituents

AgNCs have emerged as a promising substitute for antibiotics in the battle against various pathogenic bacteria. In addition to their capacity to inhibit the growth [78] of multidrug-resistant strains, AgNCs have distinct properties, making them potentially useful against these pathogens [80]. First off, AgNCs are thought to act on the bacterial membrane, impact intracellular components, and modify the respiratory chain, among other methods, causing their antibacterial effects [81]. The second characteristic is that, among metallic nanocomposites, AgNCs are well-known for being the most powerful against bacteriomers and other pathogens. It is also biocompatible and simple to utilize for medical purposes [68]. The factors that have led to the promotion of AgNCs as an antibiotic substitute are discussed below.

Bacterial Tolerance

The use of nanocomposites against human pathogenic microorganisms has advanced rapidly in recent years, coinciding with observations of their positive consequences. This subject of bacterial tolerance to nanocomposites is still being researched to comprehend the mechanism underlying this learned tolerance, in addition to the precise mode of action of the nanocomposites [82].

Apart from bacterial resistance, Kaweeteerawat et al. [83] found that antibiotic efficacy could be lowered if bacteriomers had previously been treated with AgNCs. In this instance, isolates of *E. coli* and *Staphylococcus aureus* that had previously been treated with AgNCs showed resistance to ampicillin and other antibiotics, as evidenced by MIC values that were 2–8 times higher than those of the bacteriomers that had not previously had AgNCs' treatment. The study found that bacteriomers infused with AgNCs acquired membrane-related alterations. These include decreased porosity and stiffer membranes, both of which can increase the organism's downstream antibiotic- or synthetic-antibacterial resistance.

The emergence of tolerance in bacteriomers that were progressively biocultured with different amounts of AgNCs was examined by Kūedziōra et al. [84]. Strains of *E. coli*, *Klebsiella pneumoniae*, and *Staphylococcus aureus* have been repeatedly biocultured with AgNCs and studied. The results indicated a change in the antibacterial capacity of AgNCs, which resulted in mounting MIC values. This study also discovered that extended AgNC contact may induce a reduction in the desired effect.

Bacterial Resistance

Regarding this, a number of studies examining the potential consequences of using AgNCs as antibiotic substituents have been published recently. One of the main concerns is that AgNCs may cause the emergence of resistance strains. For instance, several studies showed that certain bacteriomers showed reduced susceptibility to AgNCs following repeated and continuous exposure [6]. Panáček A, et al. [85] studied this effect when AgNCs-exposed *E. coli* and *Pseudomonas aeruginosa* were multiplied. After multiple rounds of culture, the values of MIC for *E. coli* showed a rise from 3.38 mg/ml to 13.5 mg/ml, respectively. This indicated that both of the bacteriomers under study developed a tolerance to the AgNCs.

Sublethal dosages of AgNCs—which had previously been established in the same study—were given to *E. coli* and *Staphylococcus aureus* bacteriomers for a period of five days. *E. coli* and *Staphylococcus aureus* showed an increase in their IC₅₀ values from 11.89 to 17.59 mg/ml and 6.98 to 18.09 mg/ml, respectively, suggesting that these bacteriomers are becoming more tolerant of AgNCs. This information indicates that, following successive applications, bacteriomers may have become resistant to a sublethal dose of AgNCs. Even though they were not connected to genetic changes, these reported examples of AgNCs resistance emphasize the importance of investigating doses and probable mechanisms of resistance or avoidance of resistance [86].

A recent relevant study also showed an effective alternative for treating multi-resistant

bacteriometers that doesn't result in the development of nanocomposite resistance. In this instance, ampicillin was used as a reducing and capping agent during the direct synthesis of the AgNCs. The bactericidal properties of ampicillin-AgNCs were evaluated using gram-positive and gram-negative bacteriometers that were both drug-resistant and drug-sensitive. The MIC values showed that the ampicillin-AgNCs were always more effective than ampicillin or chemically generated AgNCs [87]. An effective substitute for using AgNCs in conjunction with antibiotics is the structural alteration or coupling of AgNCs with other chemicals. This approach aimed to achieve high bactericidal activity while preventing the development of bacterial resistance [88].

Synergistic and Complementary Effects

In addition to studies that show how AgNCs induce resistant bacterial strains to emerge, other research has been published to explain how AgNCs can work in concert with other compounds. These include polymers, plant extracts, or antibiotics to create additive or synergistic effects. This could lead to the development of an alternative treatment for multidrug-resistant bacterial strains without running the risk of encouraging the emergence of new resistant strains or preventing bacteriometers from becoming resistant to AgNCs [19]. The two most researched bacteriometers are gram-positive *Staphylococcus aureus* and gram-negative *E. coli*. A number of other strains have been identified, including *Vibrio cholerae*, *Proteus mirabilis*, *Enterobacter*, *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Staphylococcus epidermidis*, and *Listeria monocytogenes*. Over time, bacteriometers have grown resistant to traditional antibiotics due to the overuse of antibiotics, which has resulted in the development of new antibiotic generations [89]. The antibacterial activity of metallic (silver, gold, and platinum) nanocomposites combined with a small amount of antibiotics is significantly increased. This is particularly true when fighting multi-strain-resistant bacteriometers, as shown in Figure 5. Because AgNCs exhibit significant antibacterial action against a variety of bacteriometers, these nanocomposites have garnered a lot of attention. When used at levels up to 350 µg per day, they have no toxic off-target effects on people. Various studies examining the antibacterial activity of AgNCs in combination with antibiotics have indicated the above fact [9].

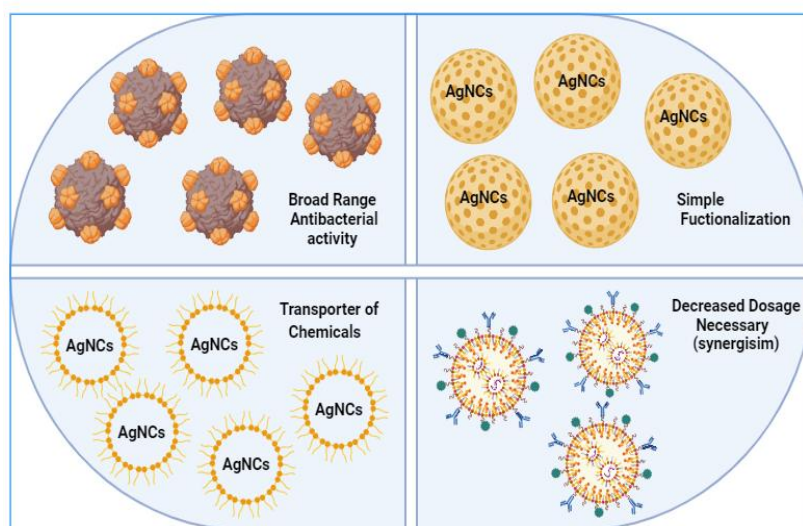


Figure 5. Advantages associated with employing AgNCs instead of or in addition to antibiotics

A recent study found that treating *E. coli*, *Salmonella typhimurium*, and *Staphylococcus aureus* with chloramphenicol-AgNCs could reduce the bacterial growth by up to 50%. However, the development of these bacteriometers was inhibited at a rate that approached 95% when kanamycin-AgNCs therapy was administered concurrently [90]. The mutual action is more effective because the AgNCs modify the integrity and action potential of the membrane, increasing cellular permeability and

making it easier for antibiotics to pass through. It should be noted that half the MIC of the antibiotic and sublethal amounts of AgNCs were used in these studies. The spleen of mice colonized with *Pseudomonas aeruginosa* was treated by the azlocillin-AgNCs conjugate, as shown by the study of Alizadeh, A. et al. [91]. The dosage of biocompatible AgNCs has shown synergistic effects with antibiotics of various classes, improving bacterial death, including both gram-positive and gram-negative bacteriomers [92].

AgNCs in combination with the antibiotics vancomycin and amikacin shown synergistic activity against gram-positive and gram-negative bacteria, respectively, in a separate study. The zone of inhibition test, which assessed antibacterial activity, showed that antibiotics and AgNCs might cooperate to accomplish this goal. The amount of bacterial inhibition produced by the combination of antibiotics and AgNCs was almost double that of the antibiotic used alone [93]. Green chemistry-prepared AgNCs using chitosan and brown marine algae extract are able to create stable AgNCs, with an average size of 12 nm. These nanocomposites have increased bactericidal efficacy towards infectious bacteriomers, including *Bacillus cereus* and *Salmonella enterica*. According to the results, AgNCs made with chitosan and algal extract had better bactericidal action than AgNCs or extract alone, with inhibition zones ranging between 6 and 12 mm for each of the bacteriomers under study [94].

The research shows that the AgNCs are positioned as an excellent supplement to or replacement for antibiotics. This shows that the antibacterial activity of AgNCs against human pathogenic bacteriomers is on par with or even greater than that of the antibiotics frequently used. Because of this, research has been done to assess any potential negative effects of exposure to AgNCs in addition to studies on their antibacterial capacity [95]. The goal is to determine the doses and characteristics of the nanocomposites that would be safe for use in humans.

Potential Cytotoxicity and Environmental Implications of AgNC Use

AgNPs, or silver nanocomposites, are widely employed in various applications, including wastewater treatment, food wrapping, and pharmaceuticals. because of their special physicochemical characteristics and antibacterial capabilities. However, there are serious environmental issues with their extensive use, especially in light of their ecotoxicity and future effects on ecosystems [7]. It has shown notable effectiveness in clinical settings in avoiding infections and accelerating wound healing. For example, its use in wound dressings has sped up tissue regeneration and decreased bacterial colonization. Likewise, their application in drug delivery systems has improved medicinal medicines' targeted administration and bioavailability. Notwithstanding these benefits, there is still worry about AgNPs' possible cytotoxicity to human cells and potential long-term repercussions on patients. To ensure its safe and efficient use in healthcare, these problems must be resolved [96]. However, their potential toxicity has raised significant environmental and human health concerns [97]. AgNCs can enter the human body through intravenous exposure, ingestion, inhalation, or skin contact. Once inside, they may accumulate in organs such as the kidneys, liver, lungs, and brain, leading to DNA damage, oxidative stress, and inflammation. Studies indicate that AgNPs can induce apoptosis, damage cellular membranes, and cause chronic toxicity after prolonged exposure. For instance, maternal exposure to AgNCs is linked to developmental toxicity, including neurobehavioral impairments and reproductive issues in children [96,97].

RESULT AND DISCUSSION

The evolution of resistant bacterial strains and the off-target effects associated with long-term usage constitute significant challenges to creating medications for the management of infections. Consequently, it takes interdisciplinary research projects to generate better antibacterials using different approaches. With the development of nanotechnology, it is now possible to manipulate the sizes of known antibacterial substances, like metals, to re-examine their biological properties and to accomplish delivery to particular targets and selectivity. AgNCs have shown great promise across a range of applications, including medical. They provide a new line of inquiry into a class of materials with potential uses in the biological, biomedical, and pharmaceutical fields. AgNCs have remarkable antibacterial efficacy when combined with modest amounts of antibiotics. This combination type has

been shown to produce outstanding results in vitro and has promise for effective bacterial eradication in vivo. Bacteriometers' exposure to sublethal concentrations of AgNCs must be prevented since this might promote the development of tolerance. Instead, the dosage of these agents needs to be monitored and managed. By using AgNCs, off-target effects are less likely to occur since fewer amounts of the antibiotic and AgNCs are needed to produce efficient antibacterial activity. In order to enhance their release and selectivity, AgNCs can form complexes to operate as drug or antibiotic carriers. Furthermore, AgNCs may be functionalized with a variety of substances to improve the antibacterial activity of the former particles against resistant strains and both gram-positive and gram-negative bacteriometers. According to these findings, AgNCs can be used as antibacterial agents; still, suitable usage strategies need to be investigated and created so as not to exacerbate the establishment of resistance strains. Because of their unique physicochemical features and antibacterial qualities, silver nanoparticles (AgNPs) are used extensively in industries like water treatment, agriculture, and medicine. But their widespread use has raised questions about their influence on the natural world, particularly their ecological toxicity and possible long-term repercussions on ecosystems. In order to improve AgNPs' biocompatibility and lower their toxicity, future studies should concentrate on improving their production. Green synthesis techniques, which make use of biological agents or plant extracts, present a viable way to create less hazardous and environmentally friendly nanoparticles. In order to lessen negative consequences, further research is also required to comprehend the processes of AgNP interacting with biological components, especially at molecular scale.

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CONFLICT OF INTEREST

The authors declare that there is no real, potential, or perceived conflict of interest for this article.

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