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New views on the ingenious applications of Ag nanoparticles as a sensor for antibiotic detection and as a potent antimicrobial agent: A Review

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Abstract

Nanotechnology uses exceptional approaches for the control of bacterial infections which uncovers the potential function of bio-systems at nano-scale level. Compared to silver ions, silver nanoparticles possess enhanced physicochemical stability and low bio-toxicity properties. The intrinsic chemical framework of silver nanoparticles is prone to exhibit a significant chemistry when used as sensor and as therapeutic. Nowadays, silver is used in (nano-) medicine, in the form of nanoparticles to optimize its therapeutic property for controlling infections caused by multidrug-resistant bacteria. Exclusive use of antibiotics as medicines and its discharge from the body of the infected person or animals into the sewage system has led to antimicrobial resistance. Rising resistance of antibiotics is another serious threat that may lead to pandemics. Thus, there is an urgent need to develop selective and sensitive sensors for probing antibiotics, especially to prevent human health hazards. The present review emphasizes on the recent advances of silver nanoparticles concerning two inter-related subjects, first, application as a therapeutic agent to control infections and secondly, as sensors to detect antibiotics. Moreover, the chemistry of silver nanoparticles behind its applications as sensor and bactericidal agent is described. Major challenges have been elaborated for the emergence of silver nanoparticles in the field of antibiotic detection and its use for controlling bacterial infections.

1. Introduction

There is a surge interest among the scientific community to understand the unique and inherent characteristics of nanoparticles as they behave differently from conventional matters [1]. Nanoparticles are colloidal particles that vary in size from 10 nm to 100 nm and have the ability to mimic or alter biological processes (e.g., infection, tissue engineering, de novo synthesis, etc.) [2]. In this course, the biological and medical research communities have exploited the distinctive feature of silver nanoparticles with momentous impacts for various applications [3-5]. The size-related chemical properties of silver nanoparticles signify its potentiality in research relating different subjects such as biology, physics, engineering, and material sciences. The use of silver nanoparticles in biological field has led to the development of analytical devices as well as applications for medical therapy in the healthcare industry [6,7]. Functionalized silver nanoparticles are created to put to work more reliable sensing and antibacterial systems with accurate results. There are different methods reported in literature to functionalize silver nanoparticles with compounds such as calixarenes [8,9], cyclodextrins [10,11], polymers [12,13], DNA [14,15], peptides [16,17], and many others. The inherent characteristics of silver nanoparticles and synergetic combination of the functionalized moieties makes up an enhancement in optical/catalytic/conductive/antibacterial properties. The favorable combination of physical structure and chemical functionality play a major role to rationalize the application of silver nanoparticles as an effective bactericidal agent. However, there are still unlimited combinations yet to be exploited and to document interesting applications of silver nanoparticles.

Silver nanoparticles have been exploited and demonstrated to act against burn wound infections [18,19], nosocomial infection [20], severe chronic osteomyelitis [21], and catheter-related urinary tract infections [22]. Several studies have suggested a distinct mechanism of actions to reveal the bacterial growth inhibition using silver nanoparticles. It has been suggested that silver ions react with sulfhydryl (-SH) groups of proteins which play an essential role in the suppression of bacterial activity. The interference with the intracellular cell signaling reduces the Adenosine Triphosphate (ATP) synthesis, which increases the reactive oxygen species (ROS) generation and causes cell death [23]. Yin *et al.* has reported that the microbicidal effect of silver nanoparticles is through the release of silver ions. It has been explained that the silver nanoparticles can penetrate the cell walls of the bacteria and after reactive oxygen species production, replication of deoxyribonucleic acid is interrupted by releasing silver ions [24]. This study also highlights the potency of silver nanoparticles in dentistry for improving the quality of the dental appliances.

The mechanism of antibacterial action is not yet clear, however due to broad-spectrum biomedical applications, silver nanoparticles are used as a potent anti-infection agent [25]. It is highly intrigued that silver nanoparticles have a bright future in discovering medical devices that can be used as artificial implants in the future and to minimize the reliability of antibiotics [26]. Based on this, many innovative approaches to test formulations based on silver nanoparticles possessing antimicrobial properties have been reported. Junejo *et al.* have reported that owing to extraordinary efficiency, cost-effectiveness, and reprocessing features silver nanoparticles can be massively casted-off as anti-cancerous, antiviral, antiarthropod, and antiprotozoal mediators [27].

Antibiotics are defined as a type of antimicrobial substance for fighting bacterial infections. The use of revolutionary medicines "antibiotics" in the health industry has been recommended for treating a wide range of infectious diseases in both livestock and humans [28]. As they are not fully metabolized in the body, they are released into the aquatic environment causing negative effects on the non-target species [29]. Moreover, the presence of antibiotics in global water environment has become a serious concern considering their adverse effects to the aquatic organism and human beings [30]. Due to their extensive usage and their structural complexity, fraction of antibiotics gets excreted via metabolism in the urine and feces as unchanged drug. This ultimately leads to the contamination of soil and natural water resources. Therefore, the development of sensing probes is greatly encouraged to hinder any destruction to the normal ecology.

The purpose of this mini review is to examine the recently published research (ranging from 2014-till date) on control of bacterial infections from the aspects of silver nanoparticles applied in healthcare industry. Also, recent reports and detailed overview of the ongoing efforts to antibiotic optical sensors as depicted in Figure 1. This review discusses a few representative antibiotics (tetracycline, oxytetracycline, kanamycin, streptomycin, gentamycin, tobramycin, cephalexin, amikacin). Besides, most of the valuable health related information supported by recent scientific data to fully meet the requirements of practical applications has been covered.

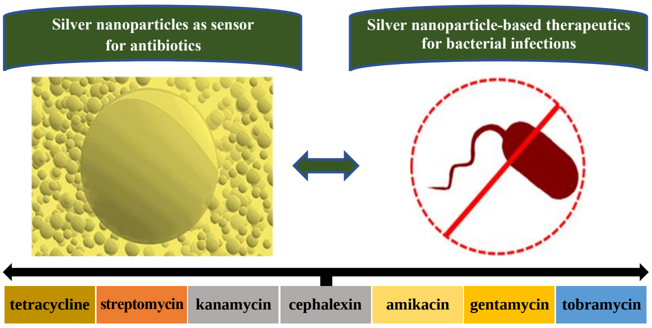

Figure 1. Application of silver nanoparticles as sensor for antibiotics and as therapeutics for bacterial infections.

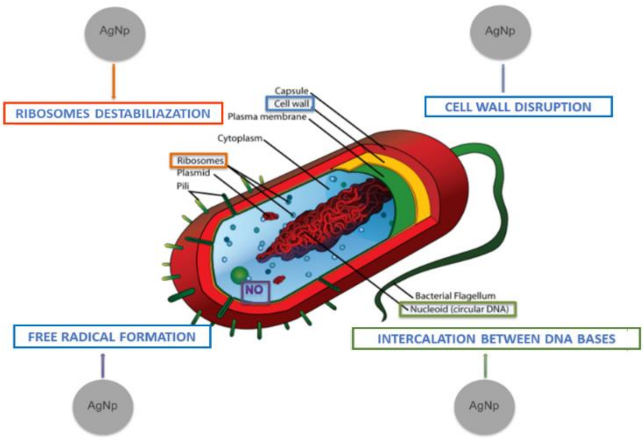

Figure 2. Mechanism of toxic action by silver nanoparticles [31].

2. Silver nanoparticle-based therapeutics for bacterial infections

The antimicrobial properties of silver (silver nitrate solution) were firstly exploited as topical germicides on ulcers and dressing wounds. It attacks bacteria either by protein coagulation or blocking sulphydryl group enzymes. Silver is also popular because it has least toxicity in the reduced stabilized state [31]. A clear representation of mechanism of AgNP's toxic action from the work of Franci *et al.* is shown in Figure 2.

Greater surface-volume ratio and a high positive charge on capped surface offer stronger affinity and membrane permeation to silver nanoparticles. This causes structural and functional alteration of subcellular microbe structures which lead to osmotic imbalance and alters the overall cell physiology. Moreover the oxygen-transporting enzymes also produces excess reactive oxygen species (ROS) that lead to membrane disruption, enzymatic and nuclear dysfunction that finally results in apoptosis [32]. Silver nanoparticles are also reported to interfere with biofilm colonization by permeating dormant bacteria within biofilms [33].

Most silver nanoparticle preparations are employed for topical use with a dosage that aims to reduce possible side effects. Few preparations include biocompatible ingredients along with antibiotic doses which renders biocompatible silver nanoparticles coupled with antibiotics [34,35]. Also, carboxymethyl cellulose (CMC) has been used as capping agent for the preparation of silver nanoparticles [36,37].

Silver nanoparticles have been used in combination with antibiotics for the development of new drugs against bacterial infections. Besides, the physicochemical properties of the silver nanomaterials and its compounds have foremost applications in the disinfectant industry. Nanocrystalline Ag connected to the surface of TiO_2 are being used for the photo-induced antibacterial studies in the presence of UV/visible light [38]. Another study reports the prevention of implant-related infections [39]. In this work, sodium triphosphate–capped silver nano-particles are immobilized onto a polyurethane film to obtain a composite film. The prepared vascular patch demonstrated excellent biocompatibility and successfully demonstrates its applicability for preventing implant-associated infections and treatment of diseased blood vessels.

Silver nanoparticles have developed new field in therapeutics with a wide range of applications such as pharmaceutical sciences and biomedicine. It was suggested that nano silver has bactericidal properties against emerging *B. megaterium* MTCC 7192 and re-emerging *P. aeruginosa* MTCC 741 through an alternation of overall surface charges and destroying membranous structure with consequent leakages of important intracellular constituents such as amino acids, fatty acids, organic acids and sugar acids [40]. Due to their large surface area-to-volume ration, silver nanoparticles in small amounts have shown great utility to render antibacterial activity. Silver nanoparticles synthesized by *Fusarium oxysporum* in combination with simvastatin have shown that only smaller doses of nanoparticles are required for the same antibacterial activity against reference and multidrug-resistant bacterial strains [41]. Silver nanoparticles in combination with cinnamaldehyde exhibited a synergistic effect against spore-forming bacterial strains [42] and the antibacterial activity of oregano essential oil combined with silver nanoparticles demonstrate anti-bacterial activity against multidrug-resistant bacteria [43]. It has been found that the synthesized nanoparticles using oregano essential oil show excellent antimicrobial activities against the multidrug-resistant bacterial strains of *E.coli, A. baumannii* which has also been supported by scanning electron microscopy (SEM). Moreover, Ampicillin, kanamycin, chloramphenicol, and erythromycin showed increased antibacterial activity when combined with AgNP against Gram-positive and Gram-negative bacteria [44]. Elmehbad *et al.* have recently reported the chitosan modified silver nano-composites to estimate the antimicrobial activity of the nanoparticles against strains of bacteria. The study further elaborated that incorporation of silver nanoparticles into chitosan derivative matrix improved its antibacterial potency. Moreover, it was studied that the antibacterial activity was due to a synergy between the antibacterial activity of both chitosan derivative and silver nanoparticles in the composites [45].

3. Silver nanoparticles as sensor for antibiotics

Optical sensors for antibiotics emerge as promising, innovative, and complementary or alternative analytical techniques for the detection of antibiotics because of their superiorities of high sensitivity and selectivity, rapid detection, easy operation, and in-situ applications [46]. Due to scattering of light at the boundary of prisms and metals, a total reflection effect will occur when the incident angle reaches the critical angle. The evanescent is coupled into metal membranes which resonates with the plasma in metal films under specific conditions. Then the energy of light wave is maximally coupled into metal films and the reflected light intensity reaches the minimum. This phenomenon is known as surface plasma resonance (SPR) [47]. Moreover, for optical sensors based on AgNPs, the interaction of the electromagnetic radiation with the electrons of the conduction band of the AgNPs determines the appearance of the localized surface plasmon resonance (LSPR) phenomenon and not of the SPR phenomenon. The LSPR phenomenon is typical of non-nanostructured metal films. In the past decades, studies have proved the potential of fluorescence spectroscopy as a monitoring and detection tool in natural and engineered systems [48-50]. Effective control of infections may reduce the need for antibiotics and prevent rapid spread of infections globally.

Kim *et al*. reported the application of gallic acid-coated silver nanoparticles for the colorimetric detection of aminoglycoside antibiotics [51]. The nanoparticles showed high sensitivity towards streptomycin and determined its analysis in water, serum, and milk samples with limit of detection (LOD) of about 36, 138, and 179 pM, respectively. Shah *et al*. reported the detection of gentamicin, a broad spectrum antibiotic belonging to the aminoglycoside class using methyl gallate reduced and stabilized silver nanoparticles (MG-AgNPs) [52]. Compared to other instrumental methods for gentamicin determination, MG-AgNPs showed low limit of detection and quantification using by spectrophotometric method. The surface plasmon resonance band of the nanoparticles was disturbed with a visible band broadening and bathochromic shift. The complexation mechanism between the nanoparticles and gentamicin has been depicted in Figure 3.

Tobramycin is an inhaled water-soluble aminoglycoside antibiotic and is used to treat bacterial infections of the eyes. Jouyban *et al*. developed a colorimetric nanoprobe for the quantification of tobramycin in exhaled breath condensate using silver nanoparticles modified with sodium dodecyl sulfate [53]. The proposed mechanism for tobramycin determination is based on the aggregation of the nanoparticles with different concentrations of tobramycin in the presence of sodium metaborate.

Cephalexin, belongs to α-aminocephalosporins class of antibiotics which have proved effective for the treatment of heart diseases. Malik *et al*. have proposed for the first time a colorimetric sensor for the detection of cephalexin based on polymer stabilized silver nanoparticles using two-phase one-pot protocol method [54].

Doxycycline belongs to class of tetracycline broad spectrum antibiotic and acts against both Gram negative and positive bacteria. Ali *et al.* designed a simple strategy for the green synthesis and detection of doxycycline using anionic surfactant sodium bis 2-ethylhexyl-sulfosuccinate based silver nanoparticles [55]. The developed sensor has a detection limit for doxycycline, as lowest as 0.2 μM within 15 min response time. An interesting and new detection protocol was developed by Chamsaz *et al*. for the sensitive determination of oxytetracycline (OTC) at nanomolar levels. The sensor was based on OTC-Eu^{3+} complex as a fluorescence probe and silver nanoparticles as a quencher [56]. This approach was successfully utilized for determination of OTC in milk and tablet samples.

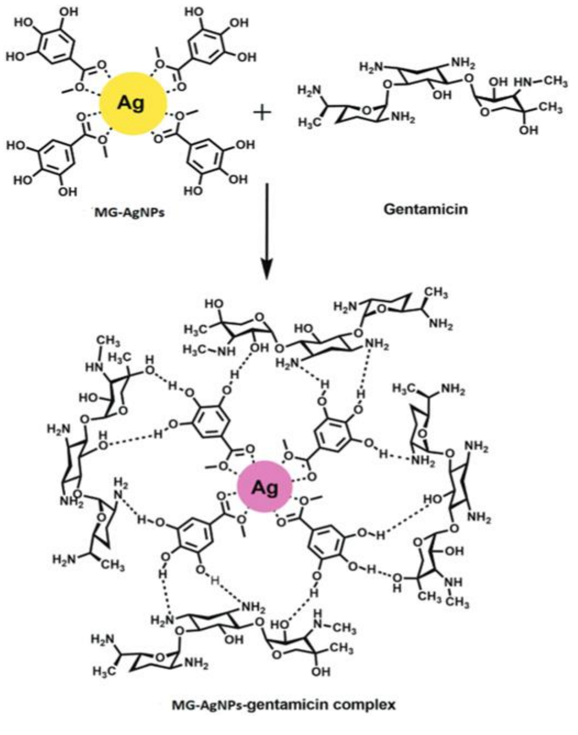

Figure 3. Silver nanoparticles: Colorimetric probe for gentamicin [52] with permission from the Centre National de la Recherche Scientifique (CNRS) and The Royal Society of Chemistry.

4. Chemistry of silver nanoparticles

There is drastic and noticeable change in different range of factors when a bulk atom is translated to its nanoscale form. Particularly, the study of the electronic and chemical structures become more relevant to nominate a reliable application of the material (Figure 4).

The intrinsic chemical framework of silver nanoparticles is prone to exhibit a significant chemistry when used for a biomedical application. For instance, antimicrobial properties of silver nanoparticles with different shapes and sizes were studied by Ashkarran and co-workers, and the formation of nanoparticle protein corona at the surface of silver nanoparticles were evaluated [57]. The importance of the work can be revealed by the study that the biological entity such as cells, tissues, and organs, do not interact with the original pristine surface of the nanoparticles, but find a new biological entity of the nanoparticles due to the formation of protein corona at the surface. Along the same lines, the concentration and exposure time of silver nanoparticles capped with cationic and non-ionic stabilizing agents were studied by Alkawareek *et al.* to understand an alternative antibacterial approach by an *in situ* generation of the bactericidal hydroxyl radicals using Fenton-like reaction between silver nanoparticles and hydrogen peroxide [58].

Silver-zwitterion nanocomposite as an antibacterial nanomedicine has been studied by Qiao *et al.* which speculates that silver nanoparticles with pH induced charge switchable activities can be used to decrease cytotoxicity towards mammalian cells in neutral solutions while increasing their toxicity against bacteria in an acidic microenvironment [59]. The pH activated enhanced antibacterial behaviour is attributed to the positive surface charge of the nanoparticles in an acidic solution which induced stronger interaction between AgNPs and microbes (negatively charged). Such newer phenomenon allows us to reveal the biogenic properties of AgNPs and to understand the pathway adopted to increase the efficiency of the nanoparticles in different microbiological environment.

The chemical fingerprints involved for the determination of antibiotic residues using silver nanoparticles is quite unique in terms of specific kind of interactions involved. In case of colorimetric sensors, the sensing process involves a visual colour change suggesting easy and a speedy result. Amongst different class of antibiotics, aminoglycosides are found to interact with the host sensing system via the multiple amine groups present in its structure. Therefore, if silver nanoparticles are capped with stabilizing or template agent which possesses –C(=O)– groups and can specifically interact with amine groups of aminoglycosides, then there are greater chances for establishing an effective sensing system. Along the same lines, Singh *et al.* [60] have reported a green protocol for synthesizing AgNPs using *Epigallocatechin gallate* as both reducing and stabilizing agent for the first time. The reduction of *Epigallocatechin gallate* by silver ions forms quinone moieties. The AgNPs showed a drastic colour change from yellow to red and established a selective detection towards kanamycin (0.96 µM) due to the specific interactions of quinone moieties with amine groups in kanamycin structure. Additionally, very recently the postulation of sensing aminoglycosides based on the chemical interaction of positively charged amine groups of aminoglycosides with negatively charged AgNPs was established by the practical application of sensing kanamycin and streptomycin using chlortetracycline functionalized AgNPs [61]. The method proved to detect the aminoglycosides in elective colorimetric manner, i.e, from yellow to red even in the presence of different class of antibiotics. Such exceptional selectivity was based on the strong affinity between the chlortetracycline ligand and aminoglycosides.

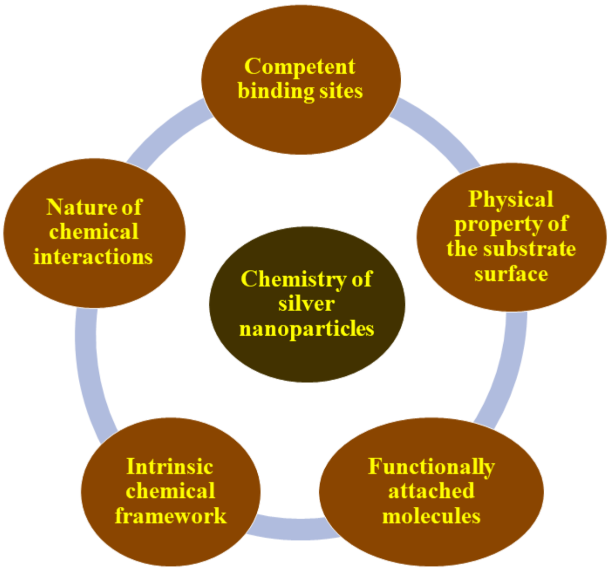

Figure 4. Segments for understanding chemistry of silver nanoparticles.

However, nature of chemical interaction plays an extensive role for selective detection of antibiotics using functionalized silver nanoparticles. For instance, the tunability and sensitivity can be modified for the sensing of antibiotics possessing amine and/or hydroxyl functionality. In the same context, Noor *et al.* [62] reported the capping of *Querecetagetin* (a flavonoid component in the extract from genus Tagetes, common name, marigold) on AgNPs could exhibit colorimetric selective detection of amoxicillin. The competent binding sites on Querecetagetin functionalized AgNPs caused hydrogen bonding between its hydroxyl group and hydroxyl/amino groups of amoxicillin. Alternatively, in case of gentamycin as an aminoglycoside, hydrogen bonding linkage between the OH groups of methyl gallate used to coat AgNPs and amino and hydroxyl groups of gentamicin has been reported by Noor *et al.* [62]

Metal ion based chemosensors for sensing antibiotics has led tremendous turn in the chemistry of silver nanoparticles. Few lanthanide ions exhibit interactions with high number of the antibiotic functional groups via coordination. Masoomeh *et al.* reported a new and sensitive fluorescence probe for recognition of oxytetracycline (OTC) on the basis of the formation of oxytetracycline-Eu^{3+} complex and role of AgNPs as a quencher [56]. The study reports the use oxytetracycline-Eu^{3+} complex for demonstrating good selectivity toward OTC and antibiotics related to tetracycline family. Silver nanoparticles as colorimetric or fluorescent sensorial agent are potential to sense antibiotics, however in the presence of certain metal ions, the sensing phenomenon depends on the formation of metal ion-antibiotic complex. On the formation of such complex the silver nanoparticles may act as a quencher as already described in the work of Masoomeh *et al*. The essential results of such considerations in the application of silver nanoparticles as sensor for antibiotics can be used to translate the laboratory results in an optoelectronic device.

5. Major challenges

Over the years, technicians and researchers have relied upon various colorimetric protocols for the detection of antibiotics using silver nanoparticles, because the existing methods such as chromatography and voltammetry appear to be too expensive and difficult to promote for practical use in villages and remote areas. There are biosensors available commercially for antibiotic detection such the Evidence Investigator System (Randox, Crumlin, UK) for the detection of antibiotic in real samples [63]. Even with these developments, there is an urgent need to overcome important challenge, that is, the in-situ analysis of antibiotics from real samples. Unfortunately, the demonstration of sensors for antibiotic detection is restricted to the laboratory scale and therefore there is need to develop portable sensing tool for ready use. Silver nanoparticles have to some extent come to the rescue of sensing antibiotics with enhanced selectivity and sensitivity. Its potential benefits have also been exploited in the sub-fields of nanomedicine, and applied as prominent nanomaterial in biomedical and industrial sectors [64]. As mentioned above, an exact understanding of the cytotoxic mechanisms of silver nanoparticles merits future research to broaden their nanomedical applications in diagnostics, therapeutics, and pharmaceutics. Topical use of silver nanoparticles is established however more on biocompatible and oral use of silver nanoparticles is the subject of exploration. Beside the wide range of applications of silver nano-products in various fields as antimicrobial agents, the actual impact of its toxicity on a human is a significant risk factor to be addressed.

Table 1. Representation of AgNPs as antimicrobial agent using different precursor material.

Nanoparticle	**Size (nm)**	**Application/Results**	**Type of antimicrobial test**	**References**
T. cordifolia reduced AgNPs	84.84	Potential template for the design of novel antibacterial agents against emerging *B. megaterium MTCC 7192* and re-emerging *P. aeruginosa MTCC 741*	Agar well diffusion assay method Zone of inhibition: 16±1.2 mm and ±1.2 mm	[40]
Bamboo cellulose nanocrystals-AgNPs	22±7	Biocompatible complete wound healing within 18 days, and showed increased expression of collagen and growth factors	--	[65]
Chitosan/Silver nanocomposites	26.64±6.4	Combined antibacterial/tissue regeneration responses to thermal burns; exhibit high antibacterial activity against *S. aureus* and *P. aeruginosa*	Luria Bertani broth bacterial counting micro-dilution method	[66]
Collagen nanofiber-AgNP	48	Antimicrobial activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*; in vivo studies wound-healing efficacy	Mueller–Hinton broth media method MIC value of 5.8±0.3 μg·ml^{-1} and 7.4±0.2 μg·ml^{-1}	[67]
AgNP-sp and AgNRs	40-50	Effective antibacterial activity against Klebsiella pneumoniae AWD5 by showing rupture of bacterial cell wall	Disc diffusion test, MIC value of 184 μg·ml^{-1}, and 320 μg·ml^{-1} concentration of AgNP-sp, and AgNR respectively	[68]
Carboxymethyl cellulose capped AgNPs	9.5	Antimicrobial activity against different multi-drug resistant strain bacteria and yeast by automated susceptibility testing device	Twofold serial broth microdilution method, MIC value of 0.02 mg·L^{-1} and 0.01 mg·L^{-1} for candida strain	[69]
Azolla caroliniana extract capped AgNP	23	Strong antibacterial activity against the tested microbes exhibits *in vitro* cytotoxicity against lymphoma ascites cells.	--	[70]
Cyclodextrin metal-organic frameworks /AgNPs	4-5	Co-delivery of Ag NPs with sulfadiazine using CD-MOF as a carrier can significantly strengthen antibacterial effect prior to the synergistic action of superfine Ag NPs with sulfadiazine	Micro-dilution method, MIC value of 4 μg·mL^{-1} in both *E. coli* and *S.aureus*	[71]
Silver nanoparticles -jujube core extract	25-35	Antibacterial activities against *E. coli* as Gram-positive bacteria and *K. pneumoniae and S. aureus* as Gram-negative bacteria	MIC values of 1.26, 2.5 and 2.5 μg·mL^{-1}, respectively	[72]
Silver nanoparticles-*Streptomyces xinghaiensis* OF1 strain	5-20	Antibacterial activities against *Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus* and *Bacillus subtilis*	Micro-dilution method, MIC values of 64, 16, 256 and 64 μg·mL^{-1}, respectively	[73]

6. Conclusion

It is hoped that this review will stimulate further research in the field of controlling bacterial infections using silver nanoparticles as therapeutic agents. From previous studies in the literature, it is noted that modified silver nanoparticles (with phospholipid and peptides) show good biocompatibility while maintaining the potent abilities to inhibit bacterial adhesion and biofilm formation. Moreover, silver nanoparticles as a sensor for the detection of antibiotics have introduced wide scope in its applications. However, there is a scope of further modification, and such studies are still yet to come to enhance their therapeutic potential and its sensing ability. Several protocols have been adopted to sense antibiotics which challenges the development of high-performance devices. On the other hand, in combination with antibiotics, silver nanoparticles are considered promising; however, for wide range synergism of antibiotics for multiple targets, the risk of drug resistance is yet to be addressed.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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