Biogenic Nanosilver against Multidrug-Resistant Bacteria (MDRB)

Caio H. N. Barros †, Stephanie Fulaz †, Danijela Stanisic and Ljubica Tasic *

Laboratory of Chemical Biology, Institute of Chemistry, State University of Campinas, Campinas 13083-970, Brazil; caionasibarros@gmail.com (C.H.N.B.); ste.fulaz@gmail.com (S.F.); danijela.stanisic@iqm.unicamp.br (D.S.)
* Correspondence: ljubica@iqm.unicamp.br
† Present address: School of Bioprocess and Chemical Engineering, University College Dublin, Dublin D04 V1W8, Ireland

Received: 28 June 2018; Accepted: 31 July 2018; Published: 2 August 2018

Abstract: Multidrug-resistant bacteria (MDRB) are extremely dangerous and bring a serious threat to health care systems as they can survive an attack from almost any drug. The bacteria’s adaptive way of living with the use of antimicrobials and antibiotics caused them to modify and prevail in hostile conditions by creating resistance to known antibiotics or their combinations. The emergence of nanomaterials as new antimicrobials introduces a new paradigm for antibiotic use in various fields. For example, silver nanoparticles (AgNPs) are the oldest nanomaterial used for bactericide and bacteriostatic purposes. However, for just a few decades these have been produced in a biogenic or bio-based fashion. This review brings the latest reports on biogenic AgNPs in the combat against MDRB. Some antimicrobial mechanisms and possible silver resistance traits acquired by bacteria are also presented. Hopefully, novel AgNPs-containing products might be designed against MDR bacterial infections.

Keywords: silver nanoparticles; biological synthesis; multidrug-resistant bacteria

1. Introduction

Antimicrobial resistance refers to the evolutionary capacity developed by microorganisms such as bacteria, fungi, viruses, and parasites to fight and neutralize an antimicrobial agent. According to the World Health Organization (WHO) [1], the intensive use and misuse of antimicrobials has led to an expansion of the number and types of resistant organisms. Moreover, the use of sub-therapeutic antibiotic doses to prevent diseases in animal breeding to improve animal growth can select resistant microorganisms, which can possibly disseminate to humans [2].

The number of pathogens presenting multidrug resistance has had an exponential increase in recent times and is considered an important problem for public health [3]. A wide number of bacteria have been reported as multidrug-resistant (MDR), and they present a high cost of management, including medicines, staff capacity, isolation materials [4], and productivity loss [5]. For instance, in the USA, the cost of conventional tuberculosis treatment for the drug-susceptible bacterium is $17,000 and up to $482,000 for the treatment of the MDR bacterium [5]. In 2017, WHO published the first list of antibiotic-resistant pathogens offering risk to human health and, as such, the development of new drugs is crucial. Priority 1 (critical) microorganisms are carbapenem-resistant Acinetobacter baumannii; carbapenem-resistant Pseudomonas aeruginosa; and carbapenem-resistant, ESBL-producing Enterobacteriaceae. Accounting for priority 2 (high) are vancomycin-resistant Enterococcus faecium; methicillin-resistant, vancomycin-intermediate and resistant Staphylococcus aureus; clarithromycin-resistant Helicobacter pylori; fluoroquinolone-resistant Campylobacter spp.; fluoroquinolone-resistant...
Salmonellae; and cephalosporin-resistant, fluoroquinolone-resistant Neisseria gonorrhoeae. In priority 3 (medium) are penicillin-non-susceptible Streptococcus pneumoniae, ampicillin-resistant Haemophilus influenzae, and fluoroquinolone-resistant Shigella spp. [6].

The use of drugs combinations, two or more antimicrobial drugs to combat MDRB [7], is already employed in cancer therapy [8], HIV-patients [9], and malaria patients [10]. On the other hand, research groups around the globe are suggesting innovative solutions to treat resistant organisms. Xiao et al. [11] synthesized the block copolymer poly (4-piperidine lactone-b-ω-pentadecalactone) with high antibacterial activity against E. coli and S. aureus, and low toxicity to NIH-3T3 cells, and suggested that cationic block copolymer biomaterials can be employed in medicine and implants. Zoriasatein et al. [12] showed that a derivative peptide from the snake (Naja naja) has an antimicrobial effect against S. aureus, B. subtilis, E. coli, and P. aeruginosa. Al-Gbouri and Hamzah [13] reported that an alcoholic extract of Phyllanthus emblica exhibits antimicrobial activity against E. coli, S. aureus, and P. aeruginosa and it inhibits biofilm formation of P. aeruginosa. Naqvi et al. [14] suggested the combined use of biologically synthesized silver nanoparticles (AgNPs) and antibiotics to combat the MDRB.

The increasing utilization and in-depth studies of nanomaterials have brought new perspectives towards new antimicrobial materials and nanocomposites that could add-in to the MDRB pandemic that we are currently facing. Nanoparticles and nanocomposites comprising zinc oxide [15], copper oxide [16], iron oxide [17], and, especially, silver, have been widely used in textiles [18,19], dental care [20], packaging [21], paints [22], and in a whole myriad of applications. Silver nanoparticles are one of the most exploited nanomaterials for this end, as they have been used for over a century in the healing of wounds and burns. Although chemical methods were successfully employed for AgNPs synthesis, with the need to use sustainable and non-toxic methods in chemistry, a biocompatible modality of AgNPs synthesis came about by using biological routes for nanoparticle synthesis (Figure 1). Biosynthesis or bio-based synthesis of AgNPs may occur through three routes: fungal, bacterial, or by plants, for the reduction of Ag⁺ to Ag⁰. The saturation of Ag⁰ monomers in suspension eventually leads to a burst-nucleation process [23] in which nanoclusters of metallic silver are produced and stabilized by biomolecules from the biological extracts.

Figure 1. Biological extracts may be prepared from any part of plant material, or via extracellular/ intracellular processes using fungi and bacteria cultures. The extracts are rich in biomolecules such as sugars, proteins, nucleic acids, and metabolites that either have a stabilizing potential or reducing and stabilizing potential for the formation of silver nanoparticles.

The demand of products for the combat of MDR bacterial strains such as Pseudomonas aeruginosa, methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant Staphylococcus aureus (VRSA), erythromycin-resistant Streptococcus pyogenes, and ampicillin-resistant Escherichia coli [24] has led to the design of powerful antimicrobial materials that are reinforced with silver nanoparticles [25]. Today, in medicinal practice, there are wound dressings, contraceptive devices, surgical instruments, bone
prostheses, and dental implants which are coated or embedded with nanosilver [26–31]. In daily life, consumers may find nanosilver in room sprays, laundry detergents, water purification devices and paints [26,32,33]. In the final part of this review, some of the recent advances in patented technologies containing AgNPs that establish viable grounds for the development of biogenic AgNPs-containing products for MDRB eradication purposes are cited and discussed.

2. Antibiotics

Antibiotics gained popularity because of their effectiveness or activities against microorganisms, as described by Selman Waksman [34], and refers to an application, and not a class of compound or its function [35]. The first compound with antibacterial activity discovered was arsphenamine, synthesized in 1907 by Alfred Bertheim in Paul Ehrlich’s laboratory, with antisyphilitic activity identified in 1909 by Sahachiro Hata [36,37]. Classically, the golden era of antibiotics refers to the period between the 50s and 70s, when the discovery of different classes of antibiotics took place [38]. For a more detailed review of antibiotics and antibacterial drugs, see Bbosa et al., 2014 [39]. Figure 2 illustrates the main antibiotic classes and examples of compounds, with corresponding dates of discovery and resistance as first reported.

![Figure 2. Illustration of different classes of antibiotics. Antibiotics that act as bactericidal agents, i.e., cause cell death, are shown in rectangles with orange borders; antibiotics that act as bacteriostatic agents, i.e., restrict growth and reproduction, are shown in rectangles with dashed line orange borders. Years shown in blue indicate when the antibiotic class was discovered (the first number), and when resistance was first reported (the second number). The structure and years of discovery and resistance refer to the first antibiotic from each class [35,40–46].](attachment:image.png)
3. The Emerging of Antimicrobial Resistance

One of the most famous antibiotics, Penicillin, was discovered in 1928 by Alexander Fleming. In 1940, before its public use, the same group identified a bacterial penicillinase [47], an enzyme able to degrade penicillin. This fact can now be related to the number of antibiotic genes that are naturally present in microbial populations [48]. In Japan, during the 50s, genetically transferable antibiotic resistance was identified. This discovery introduced the concept that antibiotic genes could spread among a population of bacterial pathogens using bacterial conjugation [49,50]. This horizontal gene transfer is important throughout genome evolution and currently presents a serious threat [51]. The bacterial genetic elasticity prompts the acquisition of genetic material, mutational adaptations, or changes in gene expression, leading to the survival of the fittest organism and the generation of resistance to antibiotics [52]. For more details regarding antibiotic resistance development, mechanisms, emergence, and spread see further references [52–58].

Currently, we face a deficiency in the development of new antibiotics to face the growing antimicrobial resistance. The constant increment in the emergence of resistant strains has not been balanced by the availability of new therapeutic agents for many reasons [59,60]. Firstly, policy-makers want to avoid the use of new antibiotics until they are indispensable, because of the resistance development. On the other hand, society needs the pharmaceutical industry to design and develop new drugs, which should not be used. Moreover, antibiotics are used in the short-term, which does not help companies to make a sustained profit. Also, the excessive cost of development and the regulatory onus makes it difficult to attend a demand for cheap antibiotics [61]. Looking at this alarming scenario the design of new therapeutics and/or new approaches is imperative.

4. Biogenic AgNPs as a Weapon against Multidrug-Resistant Bacteria (MDRB)

Traditionally, the synthesis of AgNPs using chemical approaches has been the most explored for a better size and shape control, preparation of nanocomposites and elucidation of electronic properties. However, the necessity of applying the well-known antibacterial activity of AgNPs in biological systems propelled the development of a new synthesis approach. The biological, biogenic, or bio-based methods for AgNPs synthesis present four main advantages: (1) increased biocompatibility, once AgNPs are produced in water and capped with biomolecules such as proteins, sugars or metabolites; (2) diminished toxicity, as the reducing agents are natural compounds that usually have mild reducing strength; (3) easy production, such as preparation of an extract from fungi, bacteria or plants, followed by the addition of a silver salt (typically, silver nitrate); and (4) low cost [62]. Despite positive aspects, the lack of control of shape and size of the nanoparticles is still a challenge for biogenic synthesis methods.

Because every biological synthesis is different from another as a consequence of using distinct species, the capping agents on the surface of the nanoparticles may differ. The concept of “protein corona” [63], for instance, describes the existence and dynamics of a protein shell surrounding nanoparticles in a biological environment or after a biological synthesis [64]. The interaction of biologically synthesized AgNPs with a bacterial cell will inherently involve the contact with the microorganism and the outer biomolecule shell. Thus, this interaction is unique as new joint effects (between biomolecules and the silver itself) can arise and improve the antibacterial action due to a change in toxicity, cell uptake, and bio-distribution [65].

In the case of MDRB, the mechanism of action of AgNPs is distinct from the mechanism by which traditional antibiotics act, and thus resistance does not pose an obstacle that cannot be overcome in most cases. In the following sections, each type of biological synthesis is detailed along with a literature review of biogenic AgNPs being used against MDRB. In most of the papers reviewed, the bacterial strains used for susceptibility and antibacterial tests were clinical isolates from hospital patients, however the list of antibiotics to which the strain is resistant is not always described. Also, in many cases the strain used is standardized (ATCC strains, for example), but no details on the drug resistance
capacity are provided. Here, we emphasize the examples where the provenience and description of the bacterial strain are well detailed, along with a robust antibacterial testing methodology.

4.1. Fungal AgNPs against MDRB

The synthesis of AgNPs using fungal cells may be performed outside the cells (extracellular synthesis) or inside the cells (intracellular synthesis) [66]. The former is the most recurrent in the literature, in which a fungal filtrate is obtained after the cultivation of the microorganism and a silver salt solution is added to it. Advantages of extracellular synthesis include ease of purification (as nanoparticles are not inside or attached to the fungus), facilitated downstream processing, and improved size control [67]. Despite usually having high reproducibility, fungal syntheses are time-consuming, as the fungi grow at a slower rate when compared to bacteria or the preparation of a plant extract. Moreover, the reduction of silver ions is also a gradual process, taking up to 96 h for completion. *Fusarium oxysporum* is perhaps the most studied species for AgNPs biosynthesis [19,68]; the mechanism of nanoparticle formation involves the reduction of silver(I) by a nitrate reductase and a shuttle quinone [69]. Scandorieiro et al. [70] demonstrated the synergistic effect of *F. oxysporum* produced AgNPs with oregano essential oil against a range of antibiotic-resistant bacterial strains, including MRSA and beta-lactamase producing strains. Naqvi et al. [14] also showed the effectiveness of a synergistic approach by combining *Aspergillus flavus* produced AgNPs with well-known commercial antibiotics resulting in an increase of up to 7-fold in the area of inhibition against bacterial strains resistant to the same antibiotics. In fact, a combinational therapy is highly desirable taking into consideration the development of AgNPs tolerance in bacteria via genetic evolution [71]. Chowdhury et al. studied the effect of AgNPs synthesized by *Macrophomina phaseolina* against ampicillin and chloramphenicol resistant *E. coli* and noted plasmid fragmentation and a decrease of supercoiled plasmid content upon incubation of the circular DNA with nanoparticles [72]. On the other hand, nanoparticle attachment to the cell wall and leakage of cell components induced by *Penicillium polinicum*-produced AgNPs were observed in transmission micrographs by Neethu et al. [73], which confirms that more than one antibacterial mechanism is possible (this theme is further explored in Section 4.4). Table 1 brings a summary of fungal AgNPs and their activity against MDR bacterial strains.

### Table 1. Fungi-mediated AgNPs biosynthesis and their activity against (MDRB).

| Fungus                      | AgNPs Size (nm) | Target MDR Microorganism | Test Type | Test Result | Reference |
|-----------------------------|-----------------|--------------------------|-----------|-------------|-----------|
| *Aspergillus flavus*        | 5–30            | *E. coli*                | ZI        | 15 ± 1.5 mm | [14]      |
|                             |                 | *S. aureus*              | ZI        | 16 ± 2 mm   |           |
|                             |                 | *M. luteus*              | ZI        | 14 ± 1 mm   |           |
|                             |                 | *P. aeruginosa*          | ZI        | 14 ± 1.5 mm |           |
|                             |                 | *E. faecalis*            | ZI        | 15 ± 1.5 mm |           |
|                             |                 | *A. baumannii*           | ZI        | 15 ± 1 mm   |           |
|                             |                 | *K. pneumoniae*          | ZI        | 14 ± 0.6 mm |           |
|                             |                 | *Bacillus spp.*          | ZI        | 15 ± 1.5 mm |           |
| *Fusarium oxysporum NGD*    | 16.3–70         | *Enterobacter* sp.       | ZI        | 31 mm       | [74]      |
|                             |                 | *P. aeruginosa*          | ZI        | 20 mm       |           |
|                             |                 | *K. pneumoniae*          | ZI        | 19 mm       |           |
|                             |                 | *E. coli*                | ZI        | 2 mm        |           |
| *Trichoderma viride*        | 5–40            | *E. coli*                | ZI        | 16–28 mm (*)| [75]      |
|                             |                 | *S. typhi*               | ZI        | 19–36 mm (*)|           |
|                             |                 | *S. aureus*              | ZI        | 10–19 mm (*)|           |
|                             |                 | *M. luteus*              | ZI        | 9–17 mm (*) |           |
| *Aspergillus niger*         | 30–40           | *S. aureus*              | ZI        | 15 ± 0.23 mm|           |
|                             |                 | *B. cereus*              | ZI        | 16 ± 0.32 mm|           |
|                             |                 | *P. vulgaris*            | ZI        | 14 ± 0.26 mm|           |
|                             |                 | *E. coli*                | ZI        | 14 ± 0.44 mm|           |
|                             |                 | *V. cholerae*            | ZI        | 13 ± 0.51 mm|           |
| *Tricholoma crassum*        | 5–50            | *E. coli* (DH5α)         | ZI        | 17 ± 0.5 mm | [77]      |
|                             |                 | *A. tumefaciens* (LBA4404)| ZI        | 20 ± 0.5 mm |           |

(*) Antibiotics were tested against the same bacteria.
Table 1. Cont.

| Fungus                  | AgNPs Size (nm) | Target MDR Microorganism | Test Type a | Test Result b | Reference |
|-------------------------|-----------------|--------------------------|-------------|---------------|-----------|
| Agaricus bisporus       | -               | E. coli                  | ZI          | 14 mm         | [78]      |
|                         |                 | Klebsiella sp.           | ZI          | 15 mm         |           |
|                         |                 | Pseudomonas sp.          | ZI          | 18 mm         |           |
|                         |                 | Enterobacter sp.         | ZI          | 20 mm         |           |
|                         |                 | Proteus sp.              | ZI          | 17 mm         |           |
|                         |                 | S. aureus                | ZI          | 22 mm         |           |
|                         |                 | S. typhi                 | ZI          | 17 mm         |           |
|                         |                 | S. paratyphi             | ZI          | 17 mm         |           |
| Aspergillus clavatus    | 550–650 (AFM)   | S. aureus                | ZI          | 20.5 mm       | [79]      |
|                         |                 | S. epidermidis           | ZI          | 19 mm         |           |
| Penicillium polonicum   | 10–15           | A. baumanii              | MIC, MBC, ZI| 15.62 µg mL⁻¹ (MIC), 31.24 µg mL⁻¹ (MBC), 21.2 ± 0.4 mm (ZI) | [73] |
| Cryphonectria sp.       | 30–70           | S. aureus (ATCC-25923)   | ZI          | 16 ± 0.69 mm  | [80]      |
|                         |                 | S. typhi (ATCC-51812)    | ZI          | 12 ± 0.29 mm  |           |
|                         |                 | E. coli (ATCC-39403)     | ZI          | 13 ± 1.54 mm  |           |
| Rhizopus spp.           | 27–50           | E. coli                  | ZI          | 15–22 mm (***)| [81]      |
|                         |                 | S. aureus (MRSA 101)     | MIC, MBC    | 250 µM (MIC),|           |
|                         |                 |                          |             | 500 µM (MBC)  |           |
|                         |                 | S. aureus (MRSA 107)     | MIC, MBC    | 250 µM (MIC),|           |
|                         |                 |                          |             | 500 µM (MBC)  |           |
|                         |                 | E. coli (ESBL 167)       | MIC, MBC    | 125 µM (MIC),|           |
|                         |                 |                          |             | 125 µM (MBC)  |           |
|                         |                 | E. coli (ESBL 169)       | MIC, MBC    | 125 µM (MIC),|           |
|                         |                 |                          |             | 125 µM (MBC)  |           |
|                         |                 | E. coli (ESBL 176)       | MIC, MBC    | 125 µM (MIC),|           |
|                         |                 |                          |             | 125 µM (MBC)  |           |
|                         |                 | E. coli (ESBL 192)       | MIC, MBC    | 125 µM (MIC),|           |
|                         |                 |                          |             | 125 µM (MBC)  |           |
|                         |                 | E. coli (KPC 131)        | MIC, MBC    | 125 µM (MIC),|           |
|                         |                 |                          |             | 125 µM (MBC)  |           |
|                         |                 | E. coli (KPC 133)        | MIC, MBC    | 125 µM (MIC),|           |
|                         |                 |                          |             | 125 µM (MBC)  |           |
|                         |                 | A. baumanii              | MIC, MBC    | 125 µM (MIC),|           |
|                         |                 |                          |             | 125 µM (MBC)  |           |
|                         |                 | E. coli                  | ZI          | 15 ± 1.5 mm   |           |
|                         |                 | S. aureus                | ZI          | 16 ± 2 mm     |           |
|                         |                 | M. luteus                | ZI          | 14 ± 1 mm     |           |
|                         |                 | P. aeruginosa            | ZI          | 14 ± 1.5 mm   |           |
|                         |                 | E. faecalis              | ZI          | 15 ± 1.5 mm   |           |
|                         |                 | A. baumanii              | ZI          | 15 ± 1 mm     |           |
|                         |                 | K. pneumoniae            | ZI          | 14 ± 0.6 mm   |           |
|                         |                 | Bacillus spp.            | ZI          | 15 ± 1.5 mm   |           |
| Macrophomina phaseolina | 5–40            | E. coli (DH5α-MDR)       | ZI          | 3.0 ± 0.2 mm  | [72]      |
|                         |                 | A. tumefaciens (LBA4404-MDR) | ZI | 3.3 ± 0.2 mm  |           |

a ZI = zone of inhibition; MIC = Minimum Inhibitory Concentration; MBC = Minimum Bactericidal Concentration.;
b For tests in which more than one concentration of AgNPs was used, the best results are shown; (* Values related to a synergistic effect with distinct antibiotics; (**) Values estimated from graphs; (***) More than one bacterial isolate was used.

4.2. Bacterial AgNPs against MDRB

Similarly to fungal biosynthesis, bacterial AgNPs biosynthesis may also be performed extra- or intracellularly [82]. The former can be done by using the cell biomass, where the reducing agents are secreted by the cells and the nanoparticles formed might be attached to the bacterial wall (which can possibly extend the purification process). In contrast, using a bacterial supernatant/cell-free extract has the advantage of facilitating the downstream process and purification procedures by utilizing a sterile biomolecules-rich mixture to synthesize the nanoparticles, often with the aid of microwave [83] or light irradiation [84]. Conversely, the intracellular AgNPs synthesis takes place inside the cell, often in the periplasmic space [85]. This mechanism requires a certain metal resistance from the bacteria [86] or exposure to very low concentrations of the silver salt, as the Ag⁺ ion must be imported without causing any major damage. The biggest disadvantage of this method is the purification as the nanoparticles must be removed from the interior of the cells. Ultrasonication is usually the most common method used for this end [87].
Singh et al. [88] prepared AgNPs from the culture supernatant of *Aeromonas* sp. THG-FG1.2 extracted from soil and obtained inhibition of several bacterial strains otherwise completely insensitive to erythromycin, lincomycin, novobiocin, penicillin G, vancomycin, and oleandomycin. Desai et al. [89] reported a hydrothermal biosynthesis of AgNPs using a cell-free extract of *Streptomyces* sp. GUT 21 by autoclaving the bacterial extract along with a silver salt solution. The nanoparticles were between 20–50 nm in size and active towards MDRB up to a concentration of 10 µg mL⁻¹. Sunlight exposure is also a good methodology for AgNPs biosynthesis, as demonstrated by Manikprabhu et al. [90]. Nanoparticles were produced from *Sinomonas mesophila* MPKL 26 cell supernatant in contact with silver nitrate upon up to 20 min of sun exposure. Specific secreted extracellular compounds can also be used for AgNPs synthesis. Santos et al. [91] attribute the formation of AgNPs smaller than 10 nm to xanthan gum produced during the growth of *Xanthomonas* spp. The nanoparticles could inhibit, to a certain extent, the growth of MDR *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Table 2 brings a summary of AgNPs produced by bacteria with activity against MDRB.

| Bacteria | AgNPs Size (nm) | Target MDR Microorganism | Test Type | Test Result | Reference |
|----------|----------------|--------------------------|-----------|------------|-----------|
| *Streptomyces* | 20–70 | *K. pneumoniae* (ATCC 100603) | MIC | 4 µg mL⁻¹ | [92] |
| | | *K. pneumoniae* | MIC | 1.4 µg mL⁻¹ | |
| | | *E. coli* | MIC | 2 µg mL⁻¹ | |
| | | *Citrobacter* | MIC | 2 µg mL⁻¹ | |
| *Bacillus* sp. | 14–42 | *S. epidermidis* strain 73 (pus) | ZI | 15 mm | [93] |
| | | *S. epidermidis* strain 145 (catheter tips) | ZI | 19 mm | |
| | | *S. aureus* (MTCC 87) | ZI | 18 mm | |
| | | *S. typhi* | ZI | 13 mm | |
| | | *S. paratyphi* | ZI | 15 mm | |
| | | *V. cholerae* (MTCC 3906) | ZI | 18 mm | |
| *Bacillus cereus* | 24–46 | *E. coli* | MIC, ZI | 6.25 µg mL⁻¹ (MIC), 16 ± 1 mm (ZI) | [94] |
| | | *S. aureus* | MIC, ZI | 12.5 µg mL⁻¹ (MIC), 14 ± 1 (ZI) | |
| | | *K. pneumoniae* | MIC, ZI | >3.12 µg mL⁻¹ (MIC), 17 ± 1 mm (ZI) | |
| | | *P. aeruginosa* | MIC, ZI | 3.12 µg mL⁻¹ (MIC), 23 ± 1 mm (ZI) | |
| *Bacillus safensis* (LAU 13) | 5–95 | *E. coli* | ZI | 11–19 mm | [95] |
| | | *K. granulomatis* | ZI | 11–19 mm | |
| | | *P. vulgaris* | ZI | 11–19 mm | |
| | | *P. aeruginosa* | ZI | 11–19 mm | |
| | | *S. aureus* | ZI | 11–19 mm | |
| *Aeromonas* sp. THG-FG1.2 | 8–16 | *V. parahaemolyticus* (ATCC 2725) | ZI | 16 ± 0.1 mm | [96] |
| | | *S. enterica* (ATCC 13076) | ZI | 11 ± 0.2 mm | |
| | | *C. albicans* (KACC 30062) | ZI | 20 ± 0.1 mm | |
| | | *C. tropicalis* (KCTC 7009) | ZI | 15 ± 0.5 mm | |
| *Bacillus thuringiensis* | 15 | *E. coli* | ZI | 12 ± 1 mm (*) | [97] |
| | | *P. aeruginosa* | ZI | 16 ± 1 mm (*) | |
| | | *S. aureus* | ZI | 9 ± 1 mm (*) | |
| *Anabaena diololum* | 10–50 | *K. pneumoniae* DF22SA (HQ114261) | ZI | 36 ± 0.82 mm | [98] |
| | | *E. coli* DF32TA (HQ163793) | ZI | 33 ± 1.63 mm | |
| | | *S. aureus* DF8TA (JN642261) | ZI | 34 ± 0.81 mm | |
| *Streptomyces* sp. GUT 21 | 23–48 | *E. coli* (ATCC 9537) | MIC, ZI | 14 µg mL⁻¹ (MIC), 27 ± 0.32 mm (ZI) | [99] |
| | | *K. pneumoniae* (ATCC 109) | MIC, ZI | 12 µg mL⁻¹ (MIC), 28.50 ± 2.60 mm (ZI) | |
| | | *S. aureus* (MTCC 96) | MIC, ZI | 15 µg mL⁻¹ (MIC), 24.25 ± 2.09 mm (ZI) | |
| | | *P. aeruginosa* (MTCC 1668) | MIC, ZI | 10 µg mL⁻¹ (MIC), 10.05 ± 3.60 mm (ZI) | |
Table 2. Cont.

| Bacteria       | AgNPs Size (nm) | Target MDR Microorganism | Test Type | Test Result | Reference |
|----------------|-----------------|--------------------------|-----------|-------------|-----------|
| *Bacillus megaterium* | 80–98.56 (AFM)  | *S. pneumoniae*          | ZI        | 21 mm       | [98]      |
|                |                 | *S. typhi*               | ZI        | 18 mm       |           |
| *Xanthomonas spp.* | 5–40            | *P. aeruginosa*          | ZI        | 10.0 ± 1.0 mm | [91]     |
|                |                 | *A. baumannii*           | ZI        | 10.6 ± 0.6 mm |           |
| *Sinomonas mesophila* | 4–50            | *S. aureus*              | ZI        | 12 mm       | [90]      |
| *Bacillus flexus* | 12–65           | *E. coli*                | ZI        | 11.55 mm    | [99]      |
|                |                 | *P. aeruginosa*          | ZI        | 11.05 mm    |           |
|                |                 | *S. puegens*             | ZI        | 11.65 mm    |           |
|                |                 | *S. subtilis*            | ZI        | 11.55 mm    |           |
| *Bacillus brevis* | 41–68           | *S. aureus*              | ZI        | 19 mm       | [100]     |
| (NCIM 2533)     |                 | *S. typhi*               | ZI        | 7.5 mm      |           |

a ZI = zone of inhibition; MIC = Minimum Inhibitory Concentration; MBC = Minimum Bactericidal Concentration; b For tests in which more than one concentration of AgNPs was used, the best results are shown; (*) Values estimated from graphs.

4.3. AgNPs from Plants against MDRB

Production of AgNPs using plant extracts is perhaps the most explored method in biogenic synthesis, probably due to the easiness of the procedure and wide availability of species to work with [101]. The whole plant, the stem, pod, seeds, fruit, flowers, and, most frequently, leaves are used to prepare an extract, which may be done in cold or hot solvent and almost always utilizes water (despite the fact that organic solvent extracts have also been used). The abundance of components such as reducing sugars, ascorbic acid [102], citric acid [103], alkaloids and amino acids [104], along with slightly soluble terpenoids [105], flavonoids [106], and other metabolites in various parts of the plant may easily act as reducing agents, converting Ag⁺ to AgNPs in shorter times (when compared to fungal or bacterial syntheses). Due to the lower protein content in most plants, the capping biomolecule shell often has a significant contribution of polysaccharides [107] and other molecules. Most reports on plant biosynthesis are studies of plant species found in the surroundings of the university or city where the laboratory is located, however, in vitro-derived culture of plants can also be used for these purposes [108].

Ma et al. [107] reported on the biosynthesis of 60 nm AgNPs using polysaccharide-rich root extract of *Astragalus membranaceus* and compared the bacterial inhibition against reference strains of *E. coli*, *P. aeruginosa*, *S. aureus*, and *S. epidermidis* with clinically isolated MDR strains of these bacteria. Interestingly, the nanoparticles were slightly more active toward the resistant strains.

The nanoparticle size is known to play an important role in antibacterial activity [24], and this is no different for MDR strains. AgNPs synthesized by *Caesalpinia coriaria* leaf extract, which were 50–53 nm were shown to be more active towards MDR bacterial clinical isolates when compared to 79–99 nm AgNPs [109].

Despite the common belief that biological synthesis implies a lack of control for Ag⁺ reduction and poor shape control, Jinu et al. [110] demonstrated the synthesis of cubic and triangular shaped 20 nm AgNPs using *Solanum nigrum* leaf extract. The nanoparticles had a contributing effect along with the antimicrobial plant extract towards six MDRB strains. Moreover, these AgNPs showed antibiofilm activity against *P. aeruginosa* and *S. epidermidis*. Prasannaraj et al. [111] reported an extensive study using ten different plant species for AgNPs biosynthesis, yielding spherical, cubic, and fiber-like nanoparticles. All of them inhibited bacterial growth of clinically isolated MDR pathogens and some also displayed antibiofilm activity against *P. aeruginosa* and *S. epidermidis*. The authors correlate the results with the 3 to 4-fold increase in reactive oxygen species (ROS) by AgNPs.

Intracellular ROS production was also observed by flow cytometry for *Ocimum gratissimum* leaf extract-produced AgNPs [112]; the authors suggest that the membrane damage caused by the nanoparticles could prevent efficient electronic transport in the respiratory chain. This was confirmed...
by micrographs of MDR E. coli and S. aureus cells treated with AgNPs, which showed leakage of intracellular content and pits in the membrane.

The antibacterial properties of silver can also be delivered by silver chloride nanoparticles (AgCl-NPs), as shown by Gopinath et al. [113]. AgNPs and AgCl-NPs were produced from Cissus quadrangularis leaf extract and were active towards both Gram-negative and Gram-positive MDR strains. In this case, chloride ions were identified in the extract and attributed to the formation of AgCl nanocrystals.

Table 3 presents the gathered data on plant biosynthesis of AgNPs with the corresponding activity against MDRB.

| Plant Part | AgNPs Size (nm) | Target MDR Microorganism | Test Type | Test Result | Reference |
|------------|-----------------|--------------------------|-----------|-------------|-----------|
| Olive leaf | 20–25           | S. aureus                | ZI        | 2.4 ± 0.2 cm (*)  | [114] |
| Phyllanthus amarus Whole plant | 24 ± 8 | P. aeruginosa | MIC, ZI | 6.25–12.5 µg mL⁻¹ (MIC), 10 ± 0.53 to 21 ± 0.11 mm (ZI) | [115] |
| Corchorus capsularis leaf | 5–45 | P. aeruginosa | ZI | 17 mm | [116] |
| Tribulus terrestris fruit | 16–28 | P. aeruginosa | ZI | 10 mm | [117] |
| Garcinia mangostana leaf | 35 | E. coli | ZI | 15 mm | [118] |
| Ricinus communis leaf | 29.18 (X-ray diffraction) | B. fusiformis | ZI | 29.0 cm | [119] |
| Caesalpinia coriaria leaf | 40–52 | E. coli | ZI | 12.0 ± 0.50 mm | [109] |
| | 78–98 | E. coli | ZI | 9.6 ± 0.80 mm | [109] |
| Mimosa elengi leaf | 55–83 | K. pneumonia | ZI | 18 mm | [120] |
| Ocimum gratissimum leaf | 16 ± 2 | E. coli (MC-2) | MIC, MBC, ZI | 4 µg mL⁻¹ (MIC), 8 µg mL⁻¹ (MBC), 12 ± 0.6 mm (ZI) | [121] |
| Hydrocotyle sibthorpioides Whole plant | 13.37 ± 10 | S. aureus | ZI | 3.0 ± 0.17 mm | [121] |
| Vaccinium coromandus leaf | 10–30 | S. aureus (ATCC 25922) | MIC, MBC, ZI | 11.22 ± 0.29 mm | [122] |
| Pteropus fuscus leaf | 10.8 ± 3.54 | B. subtilis (PTCC 1431) | ZI | 9.5 mm | [123] |
| Sesbania grandiflora leaf | 10–25 | S. enterica | ZI | 15.67 ± 0.09 mm | [124] |
| Solanum nigrum leaf | 20 | K. pneumonia | ZI | 21.5 mm | [110] |
| Plant               | Part     | AgNPs Size (mm) | Target MDR Microorganism | Test Type | Test Result | Reference |
|---------------------|----------|-----------------|--------------------------|-----------|-------------|-----------|
| Cissus quindungoloris | leaf     | 15–23 (**)      | S. pgecons               | MIC, ZI   | 4 µg mL⁻¹ (MIC), 7.77 ± 0.25 mm (ZI) | [113]     |
|                     |          |                 | S. aureus               | MIC, ZI   | 3 µg mL⁻¹ (MIC), 8.83 ± 0.26 mm (ZI) |          |
|                     |          |                 | E. coli                 | MIC, ZI   | 5 µg mL⁻¹ (MIC), 7.9 ± 0.31 mm (ZI) |          |
|                     |          |                 | P. vulgaris             | MIC, ZI   | 7 µg mL⁻¹ (MIC), 8.4 ± 0.40 mm (ZI) |          |
| Cole nitida         | pod      | 12-80           | E. coli                 | ZI        | 19 ± 0.9 mm | [125]     |
|                     |          |                 | K. granulomatis         | ZI        | 11 ± 0.8 mm |          |
|                     |          |                 | P. aeruginosa           | ZI        | 28 ± 1.0 mm |          |
| Strychnos potatorum | leaf     | 28              | S. aureus               | ZI        | 8 mm        | [126]     |
|                     |          |                 | K. pneumoniae           | ZI        | 10 mm       |          |
| Alstonia scholaris  | leaf     | 80              | E. coli                 | ZI        | 10.0 ± 2.8 mm | [111]   |
|                     |          |                 | P. aeruginosa           | ZI        | 8.0 ± 1.4 mm |          |
|                     |          |                 | K. pneumoniae           | ZI        | 11.0 ± 1.0 mm|          |
|                     |          |                 | S. aureus               | ZI        | 10.0 ± 3.0 mm|          |
|                     |          |                 | P. vulgaris             | ZI        | 8.3 ± 0.6 mm |          |
|                     |          |                 | S. epidermidis          | ZI        | 10.6 ± 1.2 mm|          |
| Andrographis paniculata | leaf | 70              | E. coli                 | ZI        | 8.0 ± 1.4 mm | [111]   |
|                     |          |                 | P. aeruginosa           | ZI        | 6.7 ± 0.7 mm |          |
|                     |          |                 | K. pneumoniae           | ZI        | 9.3 ± 0.6 mm |          |
|                     |          |                 | S. aureus               | ZI        | 8.0 ± 1.0 mm |          |
|                     |          |                 | P. vulgaris             | ZI        | 8.3 ± 0.6 mm |          |
|                     |          |                 | S. epidermidis          | ZI        | 9.0 ± 1.0 mm |          |
| Aegle marmelos      | leaf     | 70              | E. coli                 | ZI        | 11.0 ± 2.8 mm | [111]   |
|                     |          |                 | P. aeruginosa           | ZI        | 9.0 ± 1.4 mm |          |
|                     |          |                 | K. pneumoniae           | ZI        | 9.3 ± 1.6 mm |          |
|                     |          |                 | S. aureus               | ZI        | 9.7 ± 1.5 mm |          |
|                     |          |                 | P. vulgaris             | ZI        | 9.7 ± 0.6 mm |          |
|                     |          |                 | S. epidermidis          | ZI        | 8.0 ± 1.0 mm |          |
| Centella asiatica   | leaf     | 90              | E. coli                 | ZI        | 12.7 ± 0.7 mm | [111]   |
|                     |          |                 | P. aeruginosa           | ZI        | 8.0 ± 1.4 mm |          |
|                     |          |                 | K. pneumoniae           | ZI        | 12.0 ± 1.0 mm|          |
|                     |          |                 | S. aureus               | ZI        | 13.0 ± 2.0 mm|          |
|                     |          |                 | P. vulgaris             | ZI        | 9.7 ± 0.6 mm |          |
|                     |          |                 | S. epidermidis          | ZI        | 14.0 ± 1.0 mm|          |
| Eclipta prostrata   | leaf     | 70              | E. coli                 | ZI        | 10.0 ± 4.0 mm | [111]   |
|                     |          |                 | P. aeruginosa           | ZI        | 8.0 ± 2.5 mm |          |
|                     |          |                 | K. pneumoniae           | ZI        | 10.0 ± 5.2 mm|          |
|                     |          |                 | S. aureus               | ZI        | 12.6 ± 4.9 mm|          |
|                     |          |                 | P. vulgaris             | ZI        | 6.6 ± 0.5 mm |          |
|                     |          |                 | S. epidermidis          | ZI        | 8.0 ± 0.0 mm |          |
| Moringa oleifera    | leaf     | 50              | E. coli                 | ZI        | 7.7 ± 0.6 mm | [111]   |
|                     |          |                 | P. aeruginosa           | ZI        | 8.0 ± 1.7 mm |          |
|                     |          |                 | K. pneumoniae           | ZI        | 7.0 ± 1.0 mm |          |
|                     |          |                 | S. aureus               | ZI        | 9.0 ± 2.6 mm |          |
|                     |          |                 | P. vulgaris             | ZI        | 7.0 ± 2.0 mm |          |
|                     |          |                 | S. epidermidis          | ZI        | 7.0 ± 0.0 mm |          |
| Thebesia populnea   | bark     | 70              | E. coli                 | ZI        | 9.0 ± 1.7 mm | [111]   |
|                     |          |                 | P. aeruginosa           | ZI        | 10.3 ± 2.1 mm|          |
|                     |          |                 | K. pneumoniae           | ZI        | 11.3 ± 1.2 mm|          |
|                     |          |                 | S. aureus               | ZI        | 9.3 ± 2.4 mm |          |
|                     |          |                 | P. vulgaris             | ZI        | 8.6 ± 1.2 mm |          |
|                     |          |                 | S. epidermidis          | ZI        | 8.6 ± 0.7 mm |          |
| Terminalia arjuna   | bark     | 70              | E. coli                 | ZI        | 8.0 ± 0.7 mm | [111]   |
|                     |          |                 | P. aeruginosa           | ZI        | 9.0 ± 2.0 mm |          |
|                     |          |                 | K. pneumoniae           | ZI        | 14.0 ± 1.0 mm|          |
|                     |          |                 | S. aureus               | ZI        | 12.7 ± 1.1 mm|          |
|                     |          |                 | P. vulgaris             | ZI        | 8.3 ± 0.6 mm |          |
|                     |          |                 | S. epidermidis          | ZI        | 9.0 ± 2.0 mm |          |
| Plumbago zeplamica  | Root bark | 90            | E. coli                 | ZI        | 8.0 ± 1.4 mm | [111]   |
|                     |          |                 | P. aeruginosa           | ZI        | 14.7 ± 0.7 mm|          |
|                     |          |                 | K. pneumoniae           | ZI        | 8.2 ± 0.8 mm | [111]   |
|                     |          |                 | S. aureus               | ZI        | 7.7 ± 0.6 mm |          |
|                     |          |                 | P. vulgaris             | ZI        | 8.3 ± 0.6 mm |          |
|                     |          |                 | S. epidermidis          | ZI        | 8.0 ± 1.0 mm |          |
| Semecarpus anacardium | nuts   | 60              | E. coli                 | ZI        | 10.0 ± 2.0 mm | [111]   |
|                     |          |                 | P. aeruginosa           | ZI        | 9.3 ± 1.5 mm |          |
|                     |          |                 | K. pneumoniae           | ZI        | 10.0 ± 1.0 mm|          |
|                     |          |                 | S. aureus               | ZI        | 7.7 ± 1.1 mm |          |
|                     |          |                 | P. vulgaris             | ZI        | 8.3 ± 0.6 mm |          |
|                     |          |                 | S. epidermidis          | ZI        | 9.3 ± 1.5 mm |          |
Table 3. Cont.

| Plant Part | Plant | AgNPs Size (nm) | Target MDR Microorganism | Test Type a | Test Result b | Reference |
|------------|-------|-----------------|--------------------------|------------|---------------|-----------|
| leaf       | Mukia scabrella | 18–21 | Acinetobacter sp. | ZI | 22 mm | [127] |
| leaf       | Phyllanthus amarus | 24 ± 8 | P. aeruginosa (*** | MIC, ZI | 6.25–12.5 µg mL⁻¹ (MIC), 21 ± 0.11 mm (ZI) | [115] |
| Seed kernel | Ricinodendron heudelotti | 89.0 | E. coli | MIC, MBC | 1.68 µg mL⁻¹ (MIC), 4.12 µg mL⁻¹ (MBC) | [128] |
| leaf       | Gnetum bucholzianum | 67.4 | E. coli | ZI | 19 mm | [129] |
| leaf       | Areca catechu | 22–40 | E. coli | ZI | 20 mm | [129] |
| Cocoa bean | Cocoa | 8.96–54.22 | S. aureus | ZI | 12 mm (*) | [130] |
| Cocoa Pod husk | Phomis bracteosa | 4–32 | S. aureus (ATCC 15522) | ZI | 13.2 ± 0.12 | [131] |
| fruit      | Momordica cymbalaria | 15.5 | S. aureus (MRSA) | ZI | 0.063 mg mL⁻¹ (MIC), 12.83 ± 0.04 mm (ZI) | [107] |
| root       | Astragalus membranaceus | 65.08 | S. aureus (MRSA) | ZI | 0.063 mg mL⁻¹ (MIC), 12.33 ± 0.29 mm (ZI) | [107] |

a ZI = zone of inhibition; MIC = Minimum Inhibitory Concentration; MBC = Minimum Bactericidal Concentration.

b For tests in which more than one concentration of AgNPs was used, the best results are shown; (*) Values estimated from graphs; (**) Silver chloride nanoparticles; (***) 15 strains were tested.

4.4. Modes of Action of AgNPs against Bacteria

As stated in previous reviews on the subject [24,133–137], the antibacterial action of silver nanoparticles involves a complex mechanism in which more than one factor can act simultaneously to contribute to an overall effect. Moreover, one must consider the existence of more than one silver species, these being the Ag⁰ in the form of nanoparticles and the Ag⁺ which is released from the surface of the nanoparticles as they are slowly oxidized.

Proteomic analysis of E. coli proteins expressed after exposure to AgNPs and Ag⁺ revealed that both have a similar mode of action, such as overexpressing envelope and heat shock proteins. However, the nanoparticles were effective at inhibiting bacteria in the nanomolar concentration, whereas the Ag⁺ ions were effective only in the micromolar range [138]. On the other hand, further reports point to the opposite direction. Ag⁺ release depends on oxidation of metallic silver by oxygen in the air; in a study where E. coli was exposed to AgNPs in anaerobic conditions, no bactericidal activity was observed, while in aerobic conditions the usual antimicrobial activity was noticed [139]. This effect can be partially explained by a strong interaction of Ag⁺ with the cell membrane and cell wall components such as proteins, phospholipids, and thiol-containing groups, as well as by a proton leakage that can...
induce cell disintegration [140]. As much as the affinity of Ag⁺ for thiol groups has been known for decades [141], just recently Liao et al. [142] demonstrated how Ag⁺ can deplete intracellular thiol content of S. aureus and bind to cysteine residues of thioredoxin reductase’s catalytic site. This enzyme is one of the most important ones related to the antioxidant mechanism and reactive oxygen species (ROS) levels regulation in bacteria. Binding to respiratory chain enzymes is also a factor for intracellular ROS increase [143]. It is worth noting, however, that the protein corona that involves AgNPs has a significant effect on silver ions release. According to a study performed by Wen et al. [144], the binding of cytoskeletal proteins to AgNPs led to a decrease in Ag⁺ leakage, which could suggest that, similarly, biogenic AgNPs that are capped by biomolecules also have a diminished Ag⁺ release and thus their antimicrobial action would rely much less on this species.

Regarding the action of the nanoparticles, their size, shape and capping molecules may play significant roles when binding to the cell wall, membrane, and their internalization. In a study performed with silver nanospheres, nanocubes, and nanowires, the latter resulted in diminished antimicrobial activity when compared to the first two due to a smaller effective contact area with the cell membrane [145]. The same explanation applies for truncated octahedral AgNPs outperforming spherical AgNPs [146]. Truncated triangular shaped AgNPs had a better performance than all the other shapes in a study conducted against E. coli [147]. Acharya et al. [148] recently reported a study on silver nanospheres and silver nanorods acting against K. pneumoniae and attributed the antibacterial activity to the [111] plane shapes, which contain the highest atomic density. Smaller sizes of nanoparticles also lead to an enhanced bactericidal effect [149,150]. This effect is due to a greater surface area in contact with the bacteria that facilitate membrane rupture and internalization [151].

Perhaps one of the most accepted antibacterial mechanisms involves the association of nanoparticles with the cell wall followed by the formation of “pits” [152] and leakage of cellular contents [153]. This corroborates with the fact that AgNPs are usually more active towards Gram-negative bacteria [154], as Gram-positive bacteria have a thicker peptidoglycan cell wall, which could act as an additional physical barrier. Once inside the bacterial cell (a process that is facilitated by sizes smaller than 5 nm [155]), small nanoparticles are able to interfere with the respiratory chain dehydrogenases [156] and also induce generation of intracellular ROS [112,157], which have the ability to cleave DNA [158] and diminish bacterial life. It must be also pointed out that the interaction of AgNPs with the media which they are suspended in has a great influence on AgNPs physicochemical properties and their action on bacterial cells [159]. Figure 3 illustrates all the major mechanisms by which AgNPs display their antibacterial action.

Figure 3. Summary of the factors affecting the antimicrobial capacity of AgNPs and main antibacterial mechanisms. Size, shape and capping agents have a significant influence on the activity against bacterial cells, which are susceptible to nanoparticles because of a strong affinity of the metal with the cell wall and membrane, as well as due to interference in the respiratory chain and generation of reactive oxygen species (ROS).
4.5. Bacterial Resistance to Silver

The increasing application of silver nanomaterials in dressings, packages, and textiles has raised concerns about the development of bacterial resistance to nanosilver, despite the good performance of AgNPs against a range of bacterial strains, as already described. In fact, one of the first reports on resistance to silver was published in 1975, when a strain of *Salmonella typhimurium* resistant to silver nitrate, mercuric chloride, and a range of common antibiotics was identified in three patients in a burn unit [160]. Decades later, this exogenous type of resistance was unveiled by Gupta et al. [161] through the isolation of the plasmid pMG101. This plasmid was identified as the carrier of a silver resistance gene *silE*, which encodes a 143-amino-acid periplasmic Ag⁺-specific protein. Upstream of *silE*, a series of genes from the Sil system encode silver efflux-related proteins, such as a protein/cation antipporter system and a P-type cation ATPase (Figure 4). Resistance to silver attributed to *sil* genes was also recently reported for clinical isolates of *Klebsiella pneumonia* and *Enterobacter cloacae* [162]. Endogenous (mutational) silver resistance may also be observed, as reported by Li et al. [163], who observed silver resistance induced in *E. coli* cells by selectively culturing bacterial cells in increasing concentrations of silver nitrate. In this case, mutant cells were deficient in major porins (OmpF and OmpC). Silver efflux is also mediated through a CusCFBA efflux pump system, which has a high amino acid sequence similarity with the Sil system, in spite of being an endogenous type of resistance [164]. Crystal structures of proteins of the CusCFBA system suggest a methionine shuttle efflux mechanism, in which Ag⁺ ions are ejected from the bacterial periplasm [165,166]. Nuclear magnetic resonance (NMR) and inductively coupled plasma mass spectrometry (ICP-MS) studies have demonstrated that silver ions may induce a histidine kinase (CuS) dimerization and this conformational change may have a reflex on the upregulation of genes encoding the CusCFBA transport system [167]. The *E. coli* gene *ybdE* belonging to the K38 chromosome was also pointed out as related exclusively to Ag⁺ resistance since its deletion in silver-resistant mutant strains had no effect on Cu⁺ resistance [168]. Graves et al. [71] recently performed an extensive study using a non-resistant *E. coli* strain for an evolutionary analysis focused on mutations acquired upon exposure to silver nitrate and silver nanoparticles. After 300 generations, the Minimum Inhibitory Concentration (MIC) (using more than one type of AgNPs) of treated bacteria was already between 1.40 and 4.70 times the MIC of control bacteria. Three main mutations were observed: (1) in the *cuS* gene, which encodes the already mentioned histidine kinase which functions as a sensor for the CusCFBA efflux pump; (2) in the *purL* gene, which encodes for an enzyme involved in *de novo* purine nucleotide biosynthesis; and (3) in the *rpoB* gene, responsible for an RNA polymerase beta subunit.

![Figure 4. Silver efflux system found in Gram-negative silver-resistant bacteria. *SilE* is a periplasmic, histidine-rich Ag⁺ binding protein; *SilS* belongs to a two-component (*SilRS*) transcription regulation system; *SilA*, *SilB*, and *SilC* comprise a three-component chemiosmotic bacterial proton/cation antiporter.](image_url)
It is worth noting, however, that most of the studies cited are related to exogenous and endogenous Ag$^+$ resistance. The release of Ag$^+$ ions by AgNPs is only one of the forms by which AgNPs might be antimicrobial, as explained in Section 4.4. Few studies have looked at resistance to silver nanoparticles. For instance, Panacek et al. [169] have observed E. coli resistance to 28 nm AgNPs in sub-MIC concentrations without any genetic changes noted in E. coli. Only a phenotypic change in production of flagellin was noted. Flagellin, an adhesive protein of the flagellum, related to biofilm formation and motility, was found to readily induce nanoparticle aggregation and attenuate their antimicrobial capacity. There is still much to be researched and discovered on outer membrane–metal interactions, especially what accounts for different capping agents, topography, and morphology of AgNPs. Also, other bacterial species and strains must be studied as to map genetic and/or phenotype modifications induced by AgNPs.

5. Nanosilver Applications in Antimicrobial Products

The well-documented antimicrobial activities of AgNPs have attracted great attention from researchers and companies and caused manufacturing of many products which are in everyday use. For instance, dressings, biomedical equipment, paints, packaging materials, and gels containing nanosilver formulations are widely used. However, the number of AgNPs-containing products that are focused on or have been tested against MDRB is still unexpressive and modest. This is even surprisingly true when it comes to biogenically or bio-based synthesized AgNPs. Nevertheless, among many patents of products containing nanosilver, there are some possible applications of patented formulations in the combat against resistant bacteria, which are summarized in Table 4.

| Patent Number | Application | Resistant Bacteria | Reference |
|---------------|-------------|--------------------|-----------|
| WO2006074117A2 | Hydrogel | E. cloacae, K. pneumoniae, E. coli, P. aeruginosa, A. Acinetobacter | [170] |
| WO2018010403A1 | Pharmaceuticals | E. cloacae, K. pneumoniae, E. coli, P. aeruginosa, A. Acinetobacter | [171] |
| US20100003296A1 | Textiles | Methicillin-resistant S. aureus (MRSA) | [172] |
| KR200384433Y1 | Apron, perfume | Methicillin-resistant S. aureus (MRSA) | [173] |
| KR100933736B1 | Detergent additive | E. coli | [174] |
| CN105412940A | General | Vancomycin-resistant Enterococcus faecalis | [175] |
| WO2005120173A2 | General | P. aeruginosa | [176] |
| US7135195B2 | General | Methicillin-resistant S. aureus (MRSA) | [177] |

Despite the controversy that involves the oral use of silver nanoparticles, a recent patent has established a preparation involving AgNPs active towards MDRB suggesting many possible forms of administration, including oral, topical, and intravenous [171]. An invention communicated by Holladay et al. [170] postulates compositions containing AgNPs that may be introduced into a hydrogel for the treatment of various types of infections and inflammations, with activity against MDR E. cloacaee, K. pneumoniae, E. coli, P. aeruginosa, and A. Acinetobacter. In fact, the well-known wound healing capacity of nanosilver is often exploited in dressings and plasters. Liang et al. [178] developed an AgNPs/chitosan composite with amphiphilic properties—a hydrophobic and waterproof surface and a hydrophilic one with a capacity to interact with water and inhibit the growth of the drugs resistant S. aureus, E. coli, and P. aeruginosa. It is important to point out that these types of dressings with asymmetric wettability properties also enhance re-epithelization and collagen deposition and might be very helpful for wound healing not just because of their antiseptic properties.

Nanocrystalline silver coatings are already available commercially, for example, ACTICOAT™ has been used against MDR P. aeruginosa in burn wound infections in rat models [179]. This dressing has also been proven to be effective against methicillin-resistant S. aureus, by inhibiting bacterial growth in burn wounds. But it also decreases the secretion and swelling of the damaged tissue areas [180], which speeds up processes of wound healing.

An invention deposited by Paknikar (2006) [176] claims the production of biologically stabilized AgNPs, which were produced from various plants parts, and their incorporation into a variety of
possible carriers, such as ointments, sprays, membranes, plasters. The nanoparticles were shown to successfully inhibit MDR strains of *P. aeruginosa* and other highly resistant bacterial strains: *E. coli* ATCC 117, *P. aeruginosa* ATCC 9027, *S. abony* NCTC 6017, *S. typhimurium* ATCC 23564, *K. aerogenes* ATCC 1950, *P. vulgaris* NCBI 4157, *S. aureus* ATCC 6538P, *B. subtilis* ATCC 6633, and *C. albicans*, and, interestingly, were non-cytotoxic towards human leukemic cells (K562), carcinoma cells (HEPG2), and mouse fibroblasts (L929) in the concentrations used against cited MRDB.

Also, there are some reports on materials that contain AgNPs, such as a multipurpose nanocomposite comprising silver nanotriangles and silicon dioxide, which was developed and tested against vancomycin-resistant bacteria *E. Faecalis* (ATCC 51299) [173]. There is a nanocomposite of silver and silver oxide active towards methicillin-resistant *S. aureus* and a broad spectrum of pathogenic bacteria associated with common infections and inflammations in humans [177].

Common household objects can also be enriched with AgNPs to enhance their antimicrobial potential; for example, nanosilver has been used as a detergent additive to enhance the antibiotic effect of the surfactant while not inducing any decrease in the detergent capability of a product [174]. The detergent can be used to disinfect resistant *E. coli* strains. Enhanced hygiene and diminished contamination were also achieved by reinforcing aprons with AgNPs; the material was successful in inhibiting methicillin-resistant *S. aureus*. Cheng and Yan [172] reported and patented the invention on antimicrobial plant fibers enriched with AgNPs that showed strong antimicrobial activity. This material may be applied in various types of linings, clothing, and even for fabricating laboratory or medical coats with improved disinfection properties and thus avoid bacterial contamination.

As stated, there are still much to be discovered and researched until novel fabrics, commodities, and/or pharmaceuticals based on biogenic or bio-based silver nanoparticles became suitable for everyday applications.

6. Conclusions

Some of the main reasons for observing the multidrug resistance in bacteria were discussed along with an introduction of biogenic silver nanoparticles as an alternative or combined technology to overcome this growing health problem. Even though bio-based silver containing nanomaterials are usually not ingested as known antibiotics, mainly due to a lack of understanding of the nanotoxicology associated with nanosilver in the bloodstream or in organs, AgNPs may be incorporated in products such as dressings, sprays, textiles, and paints for MDRB combat to a certain extent. Topical use of ointments and wound dressings have become quite common, as AgNPs not only inhibit bacteria growth but also stimulate epithelial growth and reduce swelling and secretion. Bacterial resistance to silver is a concerning perspective; however, application of bio-based AgNPs may at least postpone it because the extracts used for their synthesis might have natural antimicrobial effects that can act synergistically with the nanosilver. Moreover, combined therapies based on biogenic AgNPs and known antibiotics might be even more effective than the use of only one of them.

The development of biogenic AgNPs-containing products, which are active against MDRB, finds its main obstacle in discovering a systematic, easy to reproduce, and scaled-up process for the production of the uniform nanoparticles with desirable properties that do not vary, which is extremely hard to achieve considering the biological provenience of the extracts. By the time these processes become viable, controlled, and understood, the incorporation of the biologically synthesized nanomaterials as novel biopharmaceuticals or their use as commercial products should find many opportunities in various fields.

Author Contributions: C.H.N.B., S.F. and D.S. performed bibliographic research and wrote the first version of the manuscript. L.T. idealized and revised the manuscript and coordinated the project.

Funding: The authors acknowledge the financial supports received from the Fundação de Amparo à Pesquisa de São Paulo (Fapesp—Projects N◦: 2015/12534-5 and 2014/50867-3) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq—Project N◦: 465389/201407).

Conflicts of Interest: The authors declare no conflict of interest.
References

1. World Health Organization. 10 Facts on Antimicrobial Resistance. Available online: http://www.who.int/features/factfiles/antimicrobial_resistance/en/ (accessed on 10 June 2018).
2. Littier, H.M.; Chambers, L.R.; Knowton, K.F. Animal agriculture as a contributor to the global challenge of antibiotic resistance. *CAB Rev.* 2017, 8, 1–9. [CrossRef] [PubMed]
3. Roca, I.; Akova, M.; Baquero, F.; Carlet, J.; Cavaleri, M.; Coenen, S.; Cohen, J.; Findlay, D.; Gyssens, I.; Heure, O.E.; et al. The global threat of antimicrobial resistance: Science for intervention. *New Microbe New Infect.* 2015, 6, 22–29. [CrossRef] [PubMed]
4. Huebner, C.; Rogellin, M.; Flessa, S. Economic burden of multidrug-resistant bacteria in nursing homes in Germany: A cost analysis based on empirical data. *BJM Open* 2016, 6, e008458. [CrossRef] [PubMed]
5. Centers for Disease Control and Prevention. Drug-Resistant TB. Available online: http://www.cdc.gov/tb/topic/drtb/ (accessed on 10 June 2018).
6. World Health Organization. WHO Publishes List of Bacteria for Which New Antibiotics Are Urgently Needed. Available online: http://www.who.int/en/news-room/detail/27-02-2017-who-publishes-list-of-bacteria-for-which-new-antibiotics-are-urgently-needed (accessed on 10 June 2018).
7. Worthington, R.J.; Melander, C. Combination approaches to combat multidrug-resistant bacteria. *Trends Biotechnol.* 2013, 31, 177–184. [CrossRef] [PubMed]
8. Lane, D. Designer combination therapy for cancer. *Nat. Biotechnol.* 2006, 24, 163–164. [CrossRef] [PubMed]
9. Richman, D.D. HIV chemotherapy. *Nature* 2001, 410, 995–1001. [CrossRef] [PubMed]
10. Nosten, F.; White, M.J. Artemisinin-based combination treatment of falciparum malaria. *Am. J. Trop. Med. Hyg.* 2007, 77, 191–192.
11. Xiao, Y.; Wang, D.; Heise, A.; Lang, M. Chemo-enzymatic synthesis of poly (4-piperidine lactone-b-ω-pentadecalactone) block copolymers as biomaterials with antibacterial properties. *Biomacromolecules* 2018, 19, 2673–2681. [CrossRef] [PubMed]
12. Zoriasatein, M.; Bidhendi, S.M.; Madani, R. Evaluation of antimicrobial properties of derivative peptide of Naja naja snake’s venom. *World Fam. Med. J.* 2018, 16, 44–62.
13. Al-Gbouri, N.M.; Hamzah, A.M. Evaluation of Phyllanthus emblica extract as antibacterial and antibiofilm against biofilm formation. *TIJAS* 2018, 49, 142–151.
14. Naqvi, S.Z.H.; Kiran, U.; Ali, M.I.; Jamal, A.; Hameed, S.; Ali, N. Combined efficacy of biologically synthesized silver nanoparticles and different antibiotics against multidrug-resistant bacteria. *Int. J. Nanomed.* 2013, 8, 3187–3195. [CrossRef] [PubMed]
15. Sirelkhatim, A.; Mahmoud, S.; Seeni, A.; Kaus, N.H.M.; Ann, L.C.; Bakhori, S.K.M.; Hasan, H.; Mohamad, D. Review on zinc oxide nanoparticles: Antibiocidal activity. *Nano-Micro Lett.* 2015, 7, 219–242. [CrossRef]
16. Ingle, A.P.; Duran, N.; Rai, M. Bioactivity, mechanism of action, and cytotoxicity of copper-based nanoparticles: A review. *Appl. Microbiol. Biotechnol.* 2014, 98, 1001–1009. [CrossRef] [PubMed]
17. Dinali, R.; Ebrahiminezhad, A.; Manley-Harris, M.; Ghasemi, Y.; Berenjian, A. Iron oxide nanoparticles in modern microbiology and biotechnology. *Crit. Rev. Microb.* 2017, 43, 493–507. [CrossRef] [PubMed]
18. Dastjerdi, R.; Montazer, M. A review on the application of inorganic nano-structured materials in the modification of textiles: Focus on anti-microbial properties. *Colloids Surf. B Biointerfaces* 2010, 79, 5–18. [CrossRef] [PubMed]
19. Ballottin, D.; Fulaz, S.; Cabrini, F.; Tsukamoto, J.; Durán, N.; Alves, O.L.; Tasic, L. Antimicrobial silver nanoparticles against Candida and Xanthomonas. *Mater. Sci. Eng. C* 2017, 75, 582–589. [CrossRef] [PubMed]
20. Ertem, E.; Guut, B.; Zuber, F.; Allegri, S.; Le Ouay, B.; Mefiti, S.; Formentin, K.; Stellacci, F.; Ren, Q. Core-shell silver nanoparticles in endodontic disinfection solutions enable long-term antimicrobial effect on oral biofilms. *ACS Appl. Mater. Interfaces* 2017, 9, 34762–34772. [CrossRef] [PubMed]
21. Nakazato, G.; Kobayashi, R.; Seabra, A.B.; Duran, N. Use of nanoparticles as a potential antimicrobial for food packaging. In *Food Preservation*, 1st ed.; Grumezescu, A., Ed.; Academic Press: Cambridge, MA, USA, 2016.
22. Holtz, R.D.; Lima, B.A.; Filho, A.G.S.; Brocchi, M.; Alves, O.L. Nanostructured silver vanadate as a promising antibacterial additive to water-based paints. *Nano. NBM* 2012, 8, 935–940. [CrossRef] [PubMed]
23. LaMer, V.K.; Dinegar, R.H. Theory, production and mechanism of formation of monodispersed hydrosols. J. Am. Chem. Soc. 1950, 72, 4847–4854. [CrossRef]
24. Rai, M.K.; Deshmukh, S.D.; Ingle, A.P.; Gade, A.K. Silver nanoparticles: The powerful nanoweapon against multidrug-resistant bacteria. J. Appl. Microb. 2012, 112, 841–852. [CrossRef] [PubMed]
25. Radetic, M. Functionalization of textile materials with silver nanoparticles. J. Mater. Sci. 2013, 48, 95–107. [CrossRef]
26. Maneerung, T.; Tokura, S.; Rujiravanit, R. Impregnation of silver nanoparticles into bacterial cellulose for antimicrobial wound dressing. Carbohydr. Polym. 2008, 72, 43–51. [CrossRef]
27. Chen, J.; Han, C.M.; Lin, X.W.; Tang, Z.J.; Su, S.J. Effect of silver nanoparticles dressing on second degree burn wound. Zhonghua Wai Ke Za Zhi 2006, 44, 50–52. [PubMed]
28. Muangman, P.; Chuntarasakul, P.; Sithibram, S.; Suvanchote, S.; Benhathanung, R.; Kttidacha, S.; Rueksomtawin, S. Comparison of efficacy of 1% silver sulfadiazine and Acticoat for treatment of partial-thickness burn wounds. J. Med. Assoc. Thai. 2006, 89, 953–958.
29. Cohen, M.S.; Stern, J.M.; Vanni, A.J.; Kelley, R.S.; Field, D.; Libertino, J.A.; Summerhayes, I.C. In vitro analysis of a nanocrystalline silver-coated surgical mesh. Surg. Infect. 2007, 8, 397–403. [CrossRef] [PubMed]
30. Lansdown, A.B. Silver in health care: Antimicrobial effects and safety in use. Curr. Probl. Dermatol. 2006, 33, 17–34. [PubMed]
31. Zhang, Z.; Yang, M.; Huang, M.; Hu, Y.; Xie, J. Study on germicidal efficacy and toxicity of compound disinfectant gel of nanometer silver and chlorhexidine acetate. Chin. J. Health Lab. Technol. 2007, 17, 1403–1406.
32. Zhang, Y.; Sun, J. A study on the bio-safety for nano-silver as anti-bacterial materials. Chin. J. Med. Instrum. 2007, 31, 35–38.
33. Nowack, B.; Krug, H.F.; Height, M. 120 Years of nanosilver history: Implications for policy makers. Environ. Sci. Technol. 2011, 45, 1177–1183. [CrossRef] [PubMed]
34. Waksman, S. History of the word ‘antibiotic’. J. Hist. Med. Allied Sci. 1973, 28, 284–286. [CrossRef] [PubMed]
35. Davies, J.; Davies, D. Origins and evolution of antibiotic resistance. Microbiol. Mol. Biol. Rev. 2010, 74, 417–433. [CrossRef] [PubMed]
36. Williams, K. The introduction of ‘chemotherapy’ using arsphenamine—The first magic bullet. J. R. Soc. Med. 2009, 102, 343–348. [CrossRef] [PubMed]
37. Izumi, Y.; Isozumi, K. Modern Japanese medical history and the European influence. Keio J. Med. 2001, 50, 91–99. [CrossRef] [PubMed]
38. Amivov, R. A brief history of the antibiotic era: Lessons learned and challenges for the future. Front. Microbiol. 2010, 1, 134.
39. Bbosa, G.; Mwebaza, N.; Odda, J.; Kyegombe, D.; Ntale, M. Antibiotics/antibacterial drug use, their marketing and promotion during the post-antibiotic golden age and their role in emergence of bacterial resistance. Health 2014, 6, 410–425. [CrossRef]
40. Thal, L.; Zervos, M. Occurrence and epidemiology of resistance to virginiamycin and streptogramins. J. Antimicrob. Chemother. 1999, 43, 171–176. [CrossRef] [PubMed]
41. Manten, A.; Van Wijngaarden, L. Development of drug resistance to rifampicin. Chemotherapy 1969, 14, 93–100. [CrossRef] [PubMed]
42. Chopra, I.; Roberts, M. Tetracycline antibiotics: Mode of action, applications, molecular biology, and epidemiology of bacterial resistance. Microbiol. Mol. Biol. Rev. 2001, 65, 232–260. [CrossRef] [PubMed]
43. Kirst, H. Introduction to the macrolide antibiotics. In Macrolide Antibiotics Milestones in Drug Therapy MDT; Schönfeld, W., Kirst, H., Eds.; Birkhäuser: Basel, Switzerland, 2002; pp. 1–13.
44. Jacoby, G. Mechanisms of resistance to quinolones. Clin. Infect. Dis. 2005, 41, S120–S126. [CrossRef] [PubMed]
45. Madhavan, H.; Bagyalakshmi, R. Farewell, chloramphenicol? Is this true?: A review. J. Microbiol. Biotechnol. 2013, 3, 13–26.
46. Mutnick, A.; Enne, V.; Jones, R. Linezolid resistance since 2001: SENTRY Antimicrobial Surveillance Program. Ann. Pharmacother. 2003, 37, 769–774. [CrossRef] [PubMed]
47. Abraham, E.; Chain, E. An enzyme from bacteria able to destroy penicillin. Rev. Infect. Dis. 1940, 10, 677–678. [CrossRef]
48. D’Costa, V.; McGrann, M.; Hughes, D.; Wright, G. Sampling the antibiotic resistome. Science 2006, 311, 374–377. [CrossRef] [PubMed]
49. Davies, J. Vicious circles: Looking back on resistance plasmids. Genetics 1995, 139, 1465–1468. [PubMed]
50. Helinski, D. Introduction to plasmids: A selective view of their history. In Plasmid Biology; Funnell, B., Philips, G., Eds.; ASM Press: Washington, DC, USA, 2004; pp. 1–21.
51. Hacker, J.; Kaper, J. Pathogenicity islands and the evolution of microbes. Annu. Rev. Microbiol. 2000, 54, 641–679. [CrossRef] [PubMed]
52. Munita, J.M.; Arias, C.A. Mechanisms of Antibiotic Resistance. Microbiol. Spectr. 2016, 4, 1–37.
53. Steward, P.; Costerton, J. Antibiotic resistance of bacteria in biofilms. Lancet 2001, 358, 135–138. [CrossRef]
54. Andersson, D. Persistence of antibiotic resistant bacteria. Curr. Opin. Microbiol. 2003, 6, 452–456. [CrossRef] [PubMed]
55. Nikaido, H. Multidrug Resistance in Bacteria. Annu. Rev. Biochem. 2009, 78, 119–146. [CrossRef] [PubMed]
56. Kirbis, A.; Krizman, M. Spread of antibiotic resistant bacteria from food of animal origin to humans and vice versa. Procedia Food Sci. 2015, 5, 148–151. [CrossRef]
57. Lee Ventola, C. The Antibiotic Resistance Crisis—Part 1: Causes and Threats. Pharm. Ther. 2015, 40, 277–293.
58. Van Duin, D.; Paterson, D. Multidrug resistant bacteria in the community: Trends and lessons learned. Infect. Dis. Clin. N. Am. 2016, 30, 377–390. [CrossRef] [PubMed]
59. The World Is Running out of Antibiotics, WHO Report Confirms. Available online: http://www.who.int/news-room/detail/20-09-2017-the-world-is-running-out-of-antibiotics-who-report-confirms (accessed on 10 June 2018).
60. Davies, J. Where have all the antibiotics gone? Can. J. Infect. Dis. Med. Microbiol. 2006, 17, 287–290. [CrossRef] [PubMed]
61. Why Are There So Few Antibiotics in the Research and Development Pipeline? Available online: https://www.pharmaceutical-journal.com/news-and-analysis/features/why-are-there-so-few-antibiotics-in-the-research-and-development-pipeline/11130209.article (accessed on 10 June 2018).
62. Thakkar, K.N.; Mhatre, S.S.; Parikh, R.Y. Biological synthesis of metallic nanoparticles. Nanomed. NBM 2010, 6, 257–262. [CrossRef] [PubMed]
63. Durán, N.; Silveira, C.P.; Durán, M.; Martínez, D.S.T. Silver nanoparticle protein corona and toxicity: A mini-review. J. Nanobiotechnol. 2015, 13, 1–17. [CrossRef] [PubMed]
64. Ballottin, D.; Fulaz, S.; Souza, M.L.; Corio, P.; Rodrigues, A.G.; Souza, A.O.; Marcato, P.G.; Gomes, A.F.; Gozzo, F.; Tasic, L. Elucidating protein involvement in the stabilization of the biogenic silver nanoparticles. Nanoscale Res. Lett. 2016, 11, 1–9. [CrossRef] [PubMed]
65. Shannahan, J.H.; Podila, R.; Aldossari, A.A.; Emerson, H.; Powell, B.A.; Ke, P.C.; Rao, A.M.; Brown, J.M. Formation of a protein corona on silver nanoparticles mediates cellular toxicity via scavenger receptors. Toxicol. Sci. 2014, 143, 136–146. [CrossRef] [PubMed]
66. Rai, M.; Yadav, A.; Gade, A.K. Myconanotechnology: A new and emerging science. In Applied Mycology; Rai, M., Bridge, P.D., Eds.; CABl: Wallingford, UK, 2009; pp. 258–267.
67. Zhao, X.; Zhou, L.; Rajoka, M.S.R.; Yan, L.; Jiang, C.; Shao, D.; Zhu, J.; Shi, J.; Huang, Q.; Yang, H.; et al. Fungal silver nanoparticles: Synthesis, application and challenges. Crit. Rev. Biotechnol. 2017, 38, 817–835. [CrossRef] [PubMed]
68. Ahmad, A.; Mukherjee, P.; Senapati, S.; Mandal, D.; Khan, M.I.; Kumar, R.; Sastry, M. Extracellular biosynthesis of silver nanoparticles using the fungus Fusarium oxysporum. Colloids Surf. B 2003, 28, 313–318. [CrossRef] [PubMed]
69. Durán, N.; Marcato, P.D.; Alves, O.L.; De Souza, G.I.H.; Esposito, E. Mechanistic aspects of biosynthesis of silver nanoparticles by several Fusarium oxysporum strains. J. Nanobiotechnol. 2005, 3, 8. [CrossRef] [PubMed]
70. Scandoriero, S.; de Camargo, L.C.; Lancheros, C.A.C.; Yamada-Ogatta, S.F.; Nakamura, C.V.; de Oliveira, A.G.; Andrade, C.G.T.; Durán, N.; Nakazato, G.; Kobayashi, R.K.T. Synergistic and additive effect of oregano essential oil and biological silver nanoparticles against multidrug-resistant bacterial strains. Front. Microbiol. 2016, 7, 760. [CrossRef] [PubMed]
71. Graves, J.L., Jr.; Tajkarimi, M.; Cunningham, Q.; Campbell, A.; Nonga, H.; Harrison, S.H.; Barrick, J.E. Rapid evolution of silver nanoparticle resistance in Escherichia coli. Front. Genet. 2015, 6, 42. [CrossRef] [PubMed]
72. Chowdhury, S.; Basu, A.; Kundu, S. Green synthesis of protein capped silver nanoparticles from phytopathogenic fungus Macrophomina phaseolina (Tassi) Goid with antimicrobial properties against multidrug-resistant bacteria. Nanoscale Res. Lett. 2014, 9, 365. [CrossRef] [PubMed]
73. Neethu, S.; Midhun, S.J.; Radhakrishnan, E.K.; Jyothis, M. Green synthesized silver nanoparticles by marine endophytic fungus *Penicillium polonicum* and its antibacterial efficacy against biofilm forming, multidrug-resistant *Acinetobacter baumanii*. Microb. Pathog. 2018, 116, 263–272. [CrossRef] [PubMed]
74. Gopinath, P.M.; Narchonai, G.; Dhanasekaran, D.; Ranjani, A.; Thajuddin, N. Mycosynthesis, characterization and antibacterial properties of AgNPs against multidrug resistant (MDR) bacterial pathogens of female infertility cases. Asian J. Pharm. Sci. 2015, 10, 138–145. [CrossRef]
75. Fayaz, A.M.; Balaji, K.; Girilal, M.; Yadav, R.; Kalaichelvan, P.T.; Venketesan, R. Biogenic synthesis of silver nanoparticles and their synergistic effect with antibiotics: A study against gram-positive and gram-negative bacteria. Nanomed. NBM 2010, 6, 103–109. [CrossRef] [PubMed]
76. Bhat, M.A.; Nayak, B.K.; Nanda, A. Exploitation of filamentous fungi for biosynthesis of silver nanoparticle and its enhanced antibacterial activity. Int. J. Pharm. Biol. Sci. 2015, 6, 506–515.
77. Ray, S.; Sarkar, S.; Kundu, S. Extracellular biosynthesis of silver nanoparticles using the mycorrhizal mushroom *Tricholoma crassum* (Berk.) SACC: Its antimicrobial activity against pathogenic bacteria and fungus, including multidrug resistant plant and human bacteria. Dig. J. Nanomater. Biострукт. 2011, 6, 1289–1299.
78. Dhanasekaran, D.; Latha, S.; Saha, S.; Thajuddin, N.; Panneerselvam, A. Extracellular biosynthesis, characterisation and in-vitro antibacterial potential of silver nanoparticles using *Agaricus bisporus*. J. Exp. Nanosci. 2013, 8, 579–588. [CrossRef]
79. Saravanan, M.; Nanda, A. Extracellular synthesis of silver bionanoparticles from *Aspergillus clavatus* and its antimicrobial activity against MRSA and MRSE. Colloids Surf. B Biointerfaces 2010, 77, 214–218. [CrossRef] [PubMed]
80. Dar, M.A.; Ingle, A.; Rai, M. Enhanced antimicrobial activity of silver nanoparticles synthesized by *Cryphonectria* sp. evaluated singly and in combination with antibiotics. Nanomed. NBM 2013, 9, 105–110. [CrossRef] [PubMed]
81. Hiremath, J.; Rathod, V.; Ninganagouda, S.; Singh, D.; Prema, K. Antibacterial activity of silver nanoparticles from *Rhizopus* spp against Gram negative *E. coli*-MDR strains. J. Pure Appl. Microbiol. 2014, 8, 555–562.
82. Singh, R.; Shedalkar, U.U.; Wadhwani, S.A.; Chopade, B.A. Bacteriagenic silver nanoparticles: Synthesis, mechanism, and applications. Appl. Microbiol. Biotechnol. 2015, 99, 4579–4593. [CrossRef] [PubMed]
83. Saifuddin, N.; Wong, C.W.; Yasumira, A.A.N. Rapid biosynthesis of silver nanoparticles using culture supernatant of bacteria with microwave irradiation. E-J. Chem. 2009, 6, 61–70. [CrossRef]
84. Zhang, X.; Yang, C.; Yu, H.; Sheng, G. Light-induced reduction of silver ions to silver nanoparticles in aquatic environments by microbial extracellular polymeric substances (EPS). Water Res. 2016, 106, 242–248. [CrossRef] [PubMed]
85. Klaus, T.; Joerger, R.; Olsson, E.; Granqvist, C. Silver-based crystalline nanoparticles, microbially fabricated. Proc. Natl. Acad. Sci. USA 1999, 96, 13611–13614. [CrossRef] [PubMed]
86. Klaus-Joerger, T.; Joerger, R.; Olsson, E.; Granqvist, C. Bacteria as workers in the living factory: Metal-accumulating bacteria and their potential for materials science. Trends Biotechnol. 2001, 19, 15–20. [CrossRef]
87. Kalishwaralal, K.; Deepak, V.; Pandian, S.R.K.; Kottaisamy, M.; BarathManikanth, S.; Kartukeyan, B.; Gurunathan, S. Biosynthesis of silver and gold nanoparticles using *Brevibacterium casei* and its enhanced antibacterial activity against biofilm forming, multidrug resistant plant and human bacteria. Colloids Surf. B Biointerfaces 2010, 77, 257–262. [CrossRef] [PubMed]
88. Singh, H.; Du, J.; Yi, T. Biosynthesis of silver nanoparticles using *Aeromonas* sp. THG-FG1.2 and its antibacterial activity against pathogenic microbes. Artif. Cells Nanomed. Biotechnol. 2017, 45, 584–590. [CrossRef] [PubMed]
89. Desai, P.P.; Prabhurajeshwar, C.; Chandrakanth, K.R. Hydrothermal assisted biosynthesis of silver nanoparticles from Streptomyces sp. GUT 21 (KU500633) and its therapeutic antimicrobial activity. J. Nanostruct. Chem. 2016, 6, 235–246. [CrossRef]
90. Manikprabhu, D.; Cheng, J.; Chen, W.; Sunkara, A.K.; Mane, S.B.; Kumar, R.; Das, M.; Hozeein, W.N.; Duan, Y.; Li, W. Sunlight mediated synthesis of silver nanoparticles by a novel actinobacterium (*Simonia mesophila* MPKL 26) and its antimicrobial activity against multi drug resistant *Staphylococcus aureus*. J. Photochem. Photobiol. 2016, 158, 202–205. [CrossRef] [PubMed]
91. Santos, K.S.; Barbosa, A.M.; Costa, L.P.; Pinheiro, M.S.; Oliveira, M.B.P.P.; Padilha, F.F. Silver nanocomposite biosynthesis: Antibacterial activity against multidrug-resistant strains of *Pseudomonas aeruginosa* and *Acinetobacter baumanii*. Molecules 2016, 21, 1255. [CrossRef] [PubMed]
92. Subashini, J.; Khanna, V.G.; Kannabiran, K. Anti-ESBL activity of silver nanoparticles biosynthesized using soil *Streptomyces* species. Bioprocess Biosyst. Eng. 2014, 37, 999–1006. [CrossRef] [PubMed]
99. Priyadarshini, S.; Gopinath, V.; Priyadharshini, N.M.; MubarakAli, D.; Velusamy, P. Synthesis of anisotropic silver nanoparticles using cell extracts of *Anabaena doliolum* and screening of its antibacterial and antitumor activity. *J. Microbiol. Biotechnol.* 2014, 24, 1354–1367. [CrossRef] [PubMed]

100. Saravanan, M.; Vemuganti, A.K.; Barik, S.K. Rapid biosynthesis of silver nanoparticles from *Bacillus megaterium* (NCIM 2326) and their antibacterial activity on multi drug resistant clinical pathogens. *Colloids Surf. B Biointerfaces* 2011, 88, 325–331. [CrossRef] [PubMed]

101. Ahmed, S.; Ahmad, M.; Swami, B.L.; Ikram, S. A review on plants extract mediated synthesis of silver nanoparticles for antimicrobial applications: A green expertise. *J. Adv. Res.* 2016, 7, 17–28. [CrossRef] [PubMed]

102. Pratna, T.C.; Chandrasekaran, N.; Raichur, A.M.; Mukherjee, A. Biomimetic synthesis of silver nanoparticles by *Citrus limon* (lemon) aqueous extract and theoretical prediction of particle size. *Colloids Surf. B Biointerfaces* 2011, 82, 152–159. [CrossRef] [PubMed]

103. Singh, G.; Babele, P.K.; Shahi, S.K.; Sinha, R.P.; Tyagi, M.B.; Kumar, A. Green synthesis of silver nanoparticles using cell extracts of *Anabaena doliolum* and screening of its antibacterial and antitumor activity. *J. Microbiol. Biotechnol.* 2014, 24, 1354–1367. [CrossRef] [PubMed]

104. Makarov, V.; Love, A.; Sinitsyna, O.; Yaminsky, S.M.; Taliansky, S.; Kalinina, N. Green nanotechnologies: A synergistic reduction approach. *Langmuir* 2010, 26, 4400–4408. [CrossRef] [PubMed]

105. Singh, A.K.; Talat, M.; Singh, D.P.; Srivastava, O.N. Biosynthesis of gold and silver nanoparticles by natural precursor clove and their functionalization with amine group. *J. Nanopart. Res.* 2010, 12, 1667–1675. [CrossRef]

106. Barros, C.H.N.; Cruz, G.C.F.; Mayrink, M.; Tasic, L. Bio-based synthesis of silver nanoparticles from orange waste: Effects of distinct biomolecule coatings on size, morphology, and antimicrobial activity. *Nanotechnol. Sci. Appl.* 2018, 11, 1–14. [CrossRef] [PubMed]

107. Ma, Y.; Liu, C.; Qu, D.; Chen, Y.; Huang, M.; Liu, Y. Antibacterial evaluation of silver nanoparticles synthesized by polysaccharides from *Astragalus membranaceus* roots. *Biomed. Pharmacother.* 2017, 89, 351–357. [CrossRef] [PubMed]

108. Anjum, S.; Abbasi, B.H. Biomimetic synthesis of antimicrobial silver nanoparticles using in vitro-propagated plantlets of a medicinally important endangered species: *Phlomis bracteosa*. *Int. J. Nanomed.* 2016, 11, 1663–1675. [CrossRef]

109. Jeeva, K.; Thiyagarajan, M.; Elangovan, V.; Geetha, N.; Venkatachalam, P. *Caesalpinia coriaria* leaf extracts mediated biosynthesis of metallic silver nanoparticles and their antibacterial activity against clinically isolated pathogens. *Ind. Crops Prod.* 2012, 52, 714–720. [CrossRef]

110. Prasannaraj, G.; Venkatachalam, P. Enhanced antibacterial, anti-biofilm and antioxidant (ROS) activities of biomolecules engineered silver nanoparticles against clinically isolated Gram positive and Gram negative microbial pathogens. *J. Clust. Sci.* 2017, 28, 645–664. [CrossRef]
112. Das, B.; Dash, S.K.; Mandal, D.; Ghosh, T.; Chattopadhyay, S.; Tripathy, S.; Das, S.; Dey, S.K.; Das, D.; Roy, S. Green synthesized silver nanoparticles destroy multidrug resistant bacteria via reactive oxygen species mediated membrane damage. *Arab. J. Chem.* **2017**, *10*, 862–876. [CrossRef]

113. Gopinath, V.; Priyadarshini, S.; Priyadharshshini, N.M.; Pandian, K.; Velusamy, P. Biogenic synthesis of antibacterial silver chloride nanoparticles using leaf extracts of *Cissus quadrangularis* Linn. *Mater. Lett.* **2013**, *91*, 224–227. [CrossRef]

114. Khalil, M.M.H.; Ismail, E.H.; El-Baghdady, K.Z.; Mohamed, D. Green synthesis of silver nanoparticles using olive leaf extract and its antibacterial activity. *Arab. J. Chem.* **2014**, *7*, 1131–1139. [CrossRef]

115. Singh, K.; Panghal, M.; Kadyan, S.; Chaudhary, U.; Yadav, J.P. Green silver nanoparticles of *Phyllanthus amarus*: As an antibacterial agent against multi drug resistant clinical isolates of *Pseudomonas aeruginosa*. *J. Nanobiotechnol.* **2014**, *12*, 40. [CrossRef] [PubMed]

116. Kasithevar, M.; Periakaruppan, P.; Muthupandian, S.; Mohan, M. Antibacterial efficacy of silver nanoparticles against multi-drug resistant clinical isolates from post-surgical wound infections. *Microb. Pathog.* **2017**, *107*, 327–334. [CrossRef] [PubMed]

117. Gopinath, V.; MubarakAli, D.; Priyadarshshini, S.; Priyadharshshini, N.M.; Thajuuddin, N.; Velusamy, P. Biosynthesis of silver nanoparticles from *Tribulus terrestris* and its antimicrobial approach. *Colloids Surf. B Biointerfaces* **2012**, *96*, 69–74. [CrossRef] [PubMed]

118. Veerasamy, R.; Xin, T.Z.; Gunasagaran, S.; Xiang, T.F.W.; Yang, E.F.C.; Jeyakumar, N.; Dhanaraj, S.A. Making good use of the byproducts of cultivation: Green synthesis and antibacterial effects of silver nanoparticles using *Hydrocotyle sibthorpioides* acetate extract of *Phyllanthus amarus*. *J. Nanobiotechnol.* **2013**, *10*, 282–288. [CrossRef] [PubMed]

119. Singh, A.; Mittal, S.; Shrivastav, R.; Dass, S.; Srivastava, J.N. Biosynthesis of silver nanoparticles using *Ricinus communis* L. leaf extract and its antibacterial activity. *Dig. J. Nanomater. Biostruct.* **2012**, *7*, 1157–1163.

120. Prakash, P.; Gnanaprakasam, P.; Emmanuel, R.; Arokiyaraj, S.; Saravanan, M. Green synthesis of silver nanoparticles from leaf extract of *Mimusops elengi*, Linn. for enhanced antibacterial activity against multi drug resistant clinical isolates. *Colloids Surf. B Biointerfaces* **2013**, *108*, 255–259. [CrossRef] [PubMed]

121. Garg, M.; Devi, B.; Devi, R. In vitro antibacterial activity of biosynthesized silver nanoparticles from ethyl acetate extract of *Hydrocotyle sibthorpioides* against multidrug resistant microbes. *Asian J. Pharm. Clin. Res.* **2017**, *10*, 263–266. [CrossRef]

122. Li, K.; Ma, C.; Jian, T.; Sun, H.; Wang, L.; Xu, H.; Li, W.; Su, H.; Cheng, X. Making good use of the byproducts of cultivation: Green synthesis and antibacterial effects of silver nanoparticles using the leaf extract of blueberry. *J. Food Sci. Technol.* **2017**, *54*, 3569–3576. [CrossRef] [PubMed]

123. Mira, A.; Sarani, M.; Bazaz, M.R.; Darroudi, M. Plant-mediated biosynthesis of silver nanoparticles using *Prosopis farcta* extract and its antibacterial properties. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* **2015**, *141*, 287–291. [CrossRef] [PubMed]

124. Das, J.; Das, M.P.; Velusamy, P. *Sesbania grandiflora* leaf extract mediated green synthesis of antibacterial silver nanoparticles against selected human pathogens. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* **2013**, *104*, 265–270. [CrossRef] [PubMed]

125. Lateef, A.; Azeez, M.A.; Asafa, T.B.; Yekene, T.A.; Akinbodo, A.; Oladipo, I.C.; Azeez, L.; Ajibade, S.E.; Ojo, S.A.; Gueguim-Kana, E.B.; et al. Biogenic synthesis of silver nanoparticles using a pod extract of *Cola nitida*: Antibacterial and antioxidant activities and application as a paint additive. *J. Taibah Univ. Sci.* **2016**, *10*, 551–562. [CrossRef]

126. Kagithoju, S.; Godishala, V.; Nanna, R.S. Eco-friendly and green synthesis of silver nanoparticles using leaf extract of *Strychnos potatorum* Linn.E. and their bactericidal activities. *3 Biotech* **2015**, *5*, 709–714. [CrossRef] [PubMed]

127. Prabakar, K.; Sivalingam, P.; Rabeek, S.I.M.; Muthuselvam, M.; Devarajan, N.; Arjunan, A.; Karthick, R.; Suresh, M.M.; Wembonyama, J.P. Evaluation of antibacterial efficacy of phyto fabricated silver nanoparticles using *Mukia scabrella* (Musumusukkai) against drug resistance nosocomial gram negative bacterial pathogens. *Colloids Surf. B Biointerfaces* **2013**, *104*, 282–288. [CrossRef] [PubMed]

128. Meva, F.E.; Ebongue, C.O.; Fannang, S.V.; Segnou, M.L.; Ntoumba, A.A.; Kedi, P.B.E.; Loudang, R.N.; Wanlao, A.Y.; Mang, E.R.; Mpondo, E.A.M. Natural substances for the synthesis of silver nanoparticles against Escherichia coli: The case of *Megaephyrium macrostachyum* (Marantaceae), *Corchorus olitorus* (Tiliaceae), *Ricinodendron heudelotii* (Euphorbiaceae), *Gnetum bucholzianum* (Gnetaceae), and *Ipomoea batatas* (Convolvulaceae). *J. Nanomater.* **2017**, *2017*, 6834726.
129. Shruthi, G.; Prasad, K.S.; Vinod, T.P.; Balamurugan, V.; Shivamallu, C. Green synthesis of biologically active silver nanoparticles through a phyto-mediated approach using Areca catechu leaf extract. *ChemistrySelect* 2017, 2, 10354–10359. [CrossRef]

130. Azeez, M.A.; Lateef, A.; Asafa, T.B.; Yekeen, T.A.; Akinboro, A.; Oladipo, I.C.; Gueguim-Kana, E.B.; Beukes, L.S. Biomedical applications of cocoa bean extract-mediated silver nanoparticles as antimicrobial, larvicidal and anticoagulant agents. *J. Clust. Sci.* 2017, 28, 149–164. [CrossRef]

131. Lateef, A.; Azeez, M.A.; Asafa, T.B.; Yekeen, T.A.; Akinboro, A.; Oladipo, I.C.; Azeez, L.; Ojo, S.A.; Gueguim-Kana, E.B.; Beukes, L.S. Cocoa pod husk extract-mediated biosynthesis of silver nanoparticles: Its antimicrobial, antioxidant and larvicidal activities. *J. Nanostruct. Chem.* 2016, 6, 159–169. [CrossRef]

132. Swamy, M.K.; Akhtar, M.S.; Mohanty, S.K.; Sinniah, U.R. Synthesis and characterization of silver nanoparticles using fruit extract of *Monordica cybolbaria* and assessment of their in vitro antimicrobial, antioxidant and cytotoxicity activities. *Spectrochim. Acta A Mol. Biomol. Spectrosc.* 2015, 151, 939–944. [CrossRef] [PubMed]

133. Durán, N.; Durán, M.; Jesús, M.B.; Seabra, A.B.; Fávaro, W.J.; Nakazato, G. Silver nanoparticles: A new view on mechanistic aspects on antimicrobial activity. *Nanomed. NBM* 2016, 12, 789–799. [CrossRef] [PubMed]

134. Li, Q.; Mahendra, S.; Lyon, D.Y.; Brunet, L.; Liga, M.V.; Li, D.; Alvarez, P.J.J. Antimicrobial nanomaterials for water disinfection and microbial control: Potential applications and implications. *Water Res.* 2008, 42, 4591–4602. [CrossRef] [PubMed]

135. Manke, A.; Wang, L.; Rojas-Astudillo, Y. Mechanisms of nanoparticle-induced oxidative stress and toxicity. *Biomol. Res. Int.* 2013, 2013, 942916. [CrossRef] [PubMed]

136. Siddiqui, K.S.; Husen, A.; Rao, R.A.K. A review on biosynthesis of silver nanoparticles and their biocidal properties. *J. Nanobiotechnol.* 2018, 16, 14. [CrossRef] [PubMed]

137. Zheng, K.; Setyawati, M.I.; Leong, D.T.; Xie, J. Antimicrobial silver nanomaterials. *Coord. Chem. Rev.* 2018, 357, 1–17. [CrossRef]

138. Lok, C.; Ho, C.M.; Chen, R.; He, Q.Y.; Yu, W.Y.; Sun, H.; Tam, P.K.; Chiu, J.F.; Che, C.M. Proteomic analysis of the mode of antibacterial action of silver nanoparticles. *J. Proteome Res.* 2006, 5, 916–924. [CrossRef] [PubMed]

139. Xiu, Z.; Zhang, Q.; Puppala, H.L.; Colvin, V.L.; Alvarez, P.J.J. Negligible particle-specific antibacterial activity of silver nanoparticles. *Nano Lett.* 2012, 12, 4271–4275. [CrossRef] [PubMed]

140. Dibrov, P.; Dzioba, J.; Gosink, K.K.; Hase, C.C. Chemiosmotic mechanism of antimicrobial activity of Ag⁺ in *Vibrio cholerae*. *Antimicrob. Agents Chemother.* 2002, 46, 2668–2670. [CrossRef] [PubMed]

141. Liau, S.Y.; Read, D.C.; Pugh, W.J.; Furr, J.R.; Russell, A.D. Interaction of silver nitrate with readily identifiable groups: Relationship to the antibacterial action of silver ions. *Lett. Appl. Microbiol.* 1997, 25, 279–283. [CrossRef] [PubMed]

142. Liao, X.; Yang, F.; Li, H.; So, P.K.; Yao, Z.; Wia, W.; Sun, H. Targeting the thioredoxin reductase–thioredoxin system from *Staphylococcus aureus* by silver ions. *Inorg. Chem.* 2017, 56, 14823–14830. [CrossRef] [PubMed]

143. Holt, K.B.; Bard, A.J. Interaction of silver(I) ions with the respiratory chain of *Escherichia coli*: An electrochemical and scanning electrochemical microscopy study of the antimicrobial mechanism of micromolar Ag⁺. *Biochemistry* 2005, 44, 13214–13223. [CrossRef] [PubMed]

144. Wen, Y.; Geitner, N.K.; Chen, R.; Ding, F.; Chen, P.; Andorfer, R.E.; Govindan, P.N.; Ke, P.C. Binding of cytotoxic, anticoagulant agents. *RSC Adv.* 2013, 3, 22002–22007. [CrossRef] [PubMed]

145. Hong, X.; Wen, J.; Xiong, X.; Hu, Y. Shape effect on the antibacterial activity of silver nanoparticles synthesized via a microwave-assisted method. *Environ. Sci. Pollut. Res.* 2016, 23, 4489–4497. [CrossRef] [PubMed]

146. Alshareef, A.; Laird, K.; Cross, R.B.M. Shape-dependent antibacterial activity of silver nanoparticles on *Escherichia coli* and *Enterococcus faecium* bacterium. *Appl. Surf. Sci.* 2017, 424, 310–315. [CrossRef]

147. Pal, S.; Tak, Y.K.; Song, J.M. Does the antibacterial activity of silver nanoparticles depend on the shape of the nanoparticle? A study of the Gram-negative bacterium *Escherichia coli*. *Appl. Environ. Microb.* 2007, 73, 1712–1720. [CrossRef] [PubMed]

148. Acharya, D.; Singha, K.M.; Pandey, P.; Mohanta, B.; Rajkumari, J.; Singh, L.P. Shape dependent physical mutillation and lethal effects of silver nanoparticles on bacteria. *Sci. Rep.* 2018, 8, 201. [CrossRef] [PubMed]

149. Ivask, A.; Kurvet, I.; Kasemets, K.; Blinova, I.; Arujoa, V.; Suppi, S.; Vija, H.; Kakin, A.; Titma, T.; Heinlana, M.; et al. Size-dependent toxicity of silver nanoparticles to bacteria, yeast, algae, crustaceans and mammalian cells in vitro. *PLoS ONE* 2014, 9, e102108. [CrossRef] [PubMed]
150. Kumari, M.; Pandey, S.; Giri, V.P.; Bhattacharya, A.; Shukla, R.; Mishra, A.; Nautiyal, C.S. Tailoring shape and size of biogenic silver nanoparticles to enhance antimicrobial efficacy against MDR bacteria. Microb. Pathog. 2017, 105, 346–355. [CrossRef] [PubMed]

151. Lu, Z.; Rong, K.; Li, J.; Yang, H.; Chen, R. Size-dependent antibacterial activities of silver nanoparticles against oral anaerobic pathogenic bacteria. J. Mater. Sci. Mater. Med. 2013, 24, 1465–1471. [CrossRef] [PubMed]

152. Chen, M.; Yang, Z.; Wu, H.; Pan, X.; Xie, X.; Wu, C. Antimicrobial activity and the mechanism of silver. J. Nanomed. 2011, 6, 2873–2877.

153. Kora, A.J.; Sashidhar, R.B. Biogenic silver nanoparticles synthesized with rhamnogalacturonan gum: Antibacterial activity, cytotoxicity and its mode of action. Arab. J. Chem. 2018, 11, 313–323. [CrossRef]

154. Kim, J.S.; Kuk, E.; Yu, N.K.; Kim, J.; Park, S.J.; Lee, H.J.; Kim, S.H.; Park, Y.K.; Park, Y.H.; Hwang, C.; et al. Antimicrobial effects of silver nanoparticles. Nanomed. NBM 2007, 3, 95–101. [CrossRef] [PubMed]

155. Choi, O.; Hu, Z. Size dependent and reactive oxygen species related nanosilver toxicity to nitrifying bacteria. Environ. Sci. Technol. 2008, 42, 4583–4588. [CrossRef] [PubMed]

156. Li, W.; Xie, X.; Shi, Q.; Zeng, H.; OU-Yang, Y.; Chen, Y. Antibacterial activity and mechanism of silver nanoparticles on Escherichia coli. Appl. Microbiol. Biotechnol. 2010, 85, 1115–1122. [CrossRef] [PubMed]

157. Ahmad, A.; Wei, Y.; Syed, F.; Rehman, A.U.; Khan, A.; Ullah, S.; Yuan, Q. The effects of bacteria-nanoparticles interface on the antibacterial activity of green synthesized silver nanoparticles. Microb. Pathog. 2017, 102, 133–142. [CrossRef] [PubMed]

158. Qayyum, S.; Oves, M.; Khan, A.U. Obliteration of bacterial growth and biofilm through ROS generation by facilely synthesized green silver nanoparticles. PLoS ONE 2017, 12, e0181363. [CrossRef] [PubMed]

159. Pareek, V.; Gupta, R.; Fanwar, J. Do physico-chemical properties of silver nanoparticles decide their interaction with biological media and bactericidal action? A review. Mater. Sci. Eng. C 2018, 90, 739–749. [CrossRef] [PubMed]

160. Mchugh, G.L.; Moellering, R.C.; Hopkins, C.C.; Swartz, M.N. Salmonella typhimurium resistant to silver nitrate, chloramphenicol, and ampicillin. Lancet 1975, 1, 235–240. [CrossRef] [PubMed]

161. Gupta, A.; Matsui, K.; Lo, J.; Silver, S. Molecular basis for resistance to silver cations in Salmonella. Nat. Med. 1999, 5, 183–185. [CrossRef] [PubMed]

162. Finley, P.J.; Norton, R.; Austin, C.; Mitchell, A.; Zank, S.; Durham, P. Unprecedented silver resistance in clinically isolated Enterobacteriaceae: Major implications for burn and wound management. Antimicrob. Agents Chemother. 2015, 59, 4734–4741. [CrossRef] [PubMed]

163. Li, X.; Nikaido, H.; Williams, K.E. Silver-resistant mutants of Escherichia coli display active efflux of Ag+ and are deficient in porins. J. Bacteriol. 1997, 179, 6127–6132. [CrossRef] [PubMed]

164. Ahmad, A.; Wei, Y.; Syed, F.; Rehman, A.U.; Khan, A.; Ullah, S.; Yuan, Q. The effects of bacteria-nanoparticles interface on the antibacterial activity of green synthesized silver nanoparticles. Microb. Pathog. 2017, 102, 133–142. [CrossRef] [PubMed]

165. Su, C.; Long, F.; Zimmermann, M.T.; Rajashekar, K.R.; Jernigan, R.L.; Yu, E.W. Crystal structure of the CusB heavy-metal efflux complex of Escherichia coli. Nature 2011, 470, 558–563. [CrossRef] [PubMed]

166. Xue, Y.; Davis, A.V.; Balakrishnan, G.; Stasser, J.P.; Staehlin, B.M.; Focia, P.; Spiro, T.G.; Penner-Hahn, J.E.; O’Halloran, T.V. Cu(I) recognition via cation–π and methionine interactions in CusF. Nat. Chem. Biol. 2008, 4, 107–109. [CrossRef] [PubMed]

167. Fudigel, S.A.; McEvoy, M.M. The histidine kinase CusS senses silver ions through direct binding by its sensor domain. Biochim. Biophys. Acta 2014, 1844, 1656–1661. [CrossRef] [PubMed]

168. Franke, S.; Grass, G.; Nies, D.H. The product of the ybdE gene of the Escherichia coli chromosome is involved in detoxification of silver ions. Microbiology 2001, 147, 965–972. [CrossRef] [PubMed]

169. Panáček, A.; Kvit, E.; Smeláková, M.; Večeřová, R.; Kolář, M.; Röderová, M.; Dyčka, F.; Šebela, M.; Prucek, R.; Tomanc, O.; et al. Bacterial resistance to silver nanoparticles and how to overcome it. Nat. Nanotechnol. 2018, 13, 65–71. [CrossRef] [PubMed]

170. Holladay, R.; Moeller, W.; Mehta, D.; Brooks, J.H.J.; Roy, R.; Mortenson, M. Silver/Water, Silver Gels and Silver-Based Compositions; and Methods for Making and Using the Same. World Intellectual Property Organization 2006074117A2, 5 January 2005.

171. Jinn, L.; Qiangbai, L.; Jianchao, S. Use of Medicinal Nanomaterial Composition Dg-5 Applied to Anti-Drug Resistant Bacteria. World Intellectual Property Organization 2018010403A1, 13 July 2016.
172. Jiachong, C.; Jixiong, Y. Manufacturing Methods and Applications of Antimicrobial Plant Fibers Having Silver Particles. U.S. Patent 2010003296, 7 January 2010.

173. Nano Silver and Perfume Contain an Apron. Korean Patent 200384333Y1, 16 May 2005.

174. Method for Preparing Nano-Silver Particle and Detergent Composition by Using Them. Korean Patent 100933736B1, 26 June 2008.

175. Composite Nanometer Antibacterial Material Used for Treating Vancomycin Drug Resistant Pathogenic Bacteria. Chinese Patent 105412940A, 2 December 2015.

176. Paknikar, K.M. Anti-Microbial Activity of Biologically Stabilized Silver Nano Particles. World Intellectual Property Organization 2005120173A2, 22 December 2005.

177. Holladay, R.J.; Christensen, H.; Moeller, W.D. Treatment of Humans with Colloidal Silver Composition. U.S. Patent 7135195B2, 14 November 2006.

178. Liang, D.; Lu, Z.; Yang, H.; Gao, J.; Chen, R. Novel asymmetric wettable AgNPs/chitosan wound dressing: In vitro and in vivo evaluation. *ACS Appl. Mater. Interfaces* 2016, 8, 3958–3968. [CrossRef] [PubMed]

179. Yabanoglu, H.; Basaran, O.; Aydogan, C.; Azap, O.K.; Karakayali, F.; Moray, G. Assessment of the effectiveness of silver-coated dressing, chlorhexidine acetate (0.5%), citric acid (3%), and silver sulfadiazine (1%) for topical antibacterial effects against the multi-drug resistant *Pseudomonas aeruginosa* infecting full-skin thickness burn wounds on rats. *Int. Surg.* 2013, 98, 416–423. [PubMed]

180. Huang, Y.; Li, X.; Liao, Z.; Zhang, G.; Liu, Q.; Tang, J.; Peng, Y.; Liu, X.; Luo, Q. A randomized comparative trial between Acticoat and SD-Ag in the treatment of residual burn wounds, including safety analysis. *Burns* 2007, 33, 161–166. [CrossRef] [PubMed]

© 2018 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).