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Review

Exploitation of Antimicrobial Nanoparticles and Their Applications in Biomedical Engineering

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Abstract: Antibiotic resistance is a major threat to public health, which contributes largely to increased mortality rates and costs in hospitals. The severity and widespread nature of antibiotic resistance result in limited treatments to effectively combat antibiotic-resistant pathogens. Nanoparticles have different or enhanced properties in contrast to their bulk material, including antimicrobial efficacy towards a broad range of microorganisms. Their beneficial properties can be utilised in various bioengineering technologies. Thus, antimicrobial nanoparticles may provide an alternative to challenge antibiotic resistance. Currently, nanoparticles have been incorporated into materials, such as fibres, glass and paints. However, more research is required to elucidate the mechanisms of action fully and to advance biomedical applications further. This paper reviews the antimicrobial efficacies and the intrinsic properties of different metallic nanoparticles, their potential mechanisms of action against certain types of harmful pathogens and how these properties may be utilised in biomedical and healthcare products with the aim to reduce cross contaminations, disease transmissions and usage of antibiotics.

Keywords: antimicrobial; antibacterial; antifungal; nanomaterial; nanoparticle; bottom-up; top-down; minimum inhibitory concentration; biomedical and healthcare applications

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1. Introduction

Data collected from PubMed (Figure 1) show that published studies on 'Nanoparticles' began in 1978, which appeared to be near the time the scanning tunnelling microscope was invented. Hence, the time when surface imagining and experimental characterisations of materials were advanced to the atomic levels [1]. The ancient existence of nanomaterials is evident by the Lycurgus Cup that was made by the Romans, which dated back in the 4th century, and which was found to contain Silver–Gold alloy nanoparticles with a diameter ranging between 50 and 100 nm. Only in 1959 did Harden and Toynbee report the dichroic effect found in the Lycurgus Cup exhibited due to the presence of these nano alloy materials [2]. Since then, it took over 20 years for the elucidation and the actual conceptual ideas of Nanotechnology to be recognised. From approximately the year 2002, the number of peer-reviewed publications on Nanoparticles research went from 1000 to nearly 25,000 within the next two decades.

Nanomaterials with antimicrobial properties are known as 'antimicrobial nanoparticles' (AMNPs), such as Silver nanoparticles (Ag NPs), and have been utilised in biocides for over 120 years [3]. However, the precise antimicrobial and physiochemical properties were not investigated until the 19th century because of the lack of available technologies. In contrast, antibiotics, which are still being employed as an effective treatment for many bacterial infections, have been widely available through prescriptions. Unfortunately, the long-term and frequently inappropriate use of antibiotics had resulted in the evolution of resistant bacteria, for instance, methicillin-resistant Staphylococcus aureus (MRSA), which was first found in the United Kingdom (UK) in 1962 [4,5]. It is estimated that antibiotic-resistant pathogens were responsible for roughly 2.8 million illnesses and 35,000 annual

deaths in the United States (US) alone, causing at least USD 20 billion costs in healthcare in 2019 [6]. This was also the reason for the increase in AMNP research which has been seen in the 20th century (Figure 1—red line).

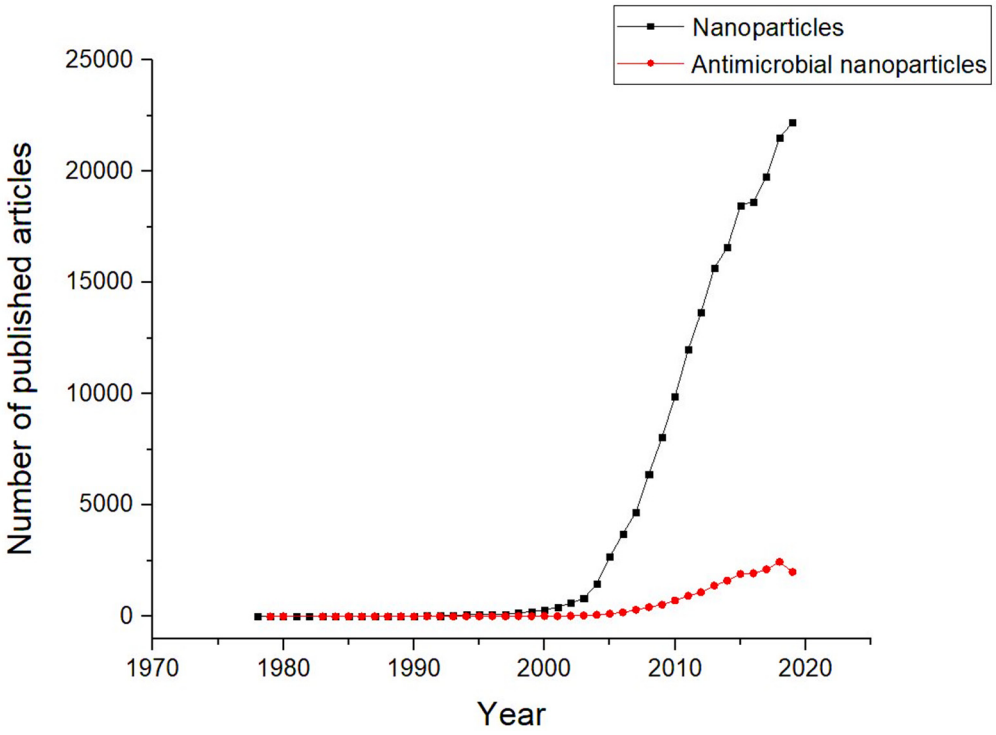

Figure 1. The graph shows articles published yearly containing keywords nanoparticles and antimicrobial nanoparticles. Data collected from PubMed.

Before the Covid-19 Pandemic, a slight decline in the prevalence of MRSA infections was reported due to the implementation of preventative measures. However, the issues over the rise in resistant bacteria were never resolved, and it is still a potential concern primarily due to the improper and overuse of antibiotics. Whilst the World Health Organisation (WHO) has introduced global plans to tackle antimicrobial resistance (AMR) [7], explorations of alternatives and new approaches to prevent disease transmissions through surface contaminations are still being urgently prioritised due to the Covid-19 situation.

After the Severe Acute Respiratory Syndrome (SARS) outbreak in 2004, an antiviral consortium was established by Ren et al., where a range of antiviral nanomaterials was engineered using the Tesima® plasma process and found to effectively inhibit SARS viruses and avian H5N1 Influenza by 80–100% through direct contact [8,9]. Certain nanomaterials (i.e., elemental Silver, Copper and their oxide derivatives) engineered using this process have recently been found also to exhibit antimicrobial activities against pathogenic bacteria, such as *Staphylococcus aureus* (*S. aureus*) and *Pseudomonas aeruginosa* (*P. aeruginosa*), which are commonly found in public settings and are responsible for many hospital-acquired infections (HAI) [10]. A recent study showed that these engineered nanomaterials can be embedded into polymer fibre and potentially be used for air/water filtration systems with the aim to prevent disease transmissions and so to reduce the demand for antibiotic utilities [11].

Although many AMNP derivatives have proven effective against one or many other pathogens, their mechanisms involved in microbial inactivation are not fully understood and have been debated in published articles [12–16]. Since there is a clear demand for nanomaterials for biomedical and healthcare applications, this paper first reviews different ways of obtaining the most common types of metallic/inorganic AMNPs (i.e., Ag, Cu, ZnO). This is then followed by an overview of the intrinsic properties that are owned by these nanoparticles but not found in their bulk derivatives, which would also reflect

the antimicrobial attributions in some of these ultra-fine particulates. To follow on, the context extends to review the possible antimicrobial mechanisms of actions involved in such AMNP.

Overall, this review acknowledges (i) the ancient existence of metallic nanoparticles, such as nano gold and silver, which were used in the 4th century; (ii) their early applications as biocides for over 120 years and as medical treatments (e.g., Collargol, Argyrol, Protargol) since the 19th century; (iii) their intrinsic properties, including antimicrobial activities, which are not found in their counter bulk materials. This article has also highlighted that nano silver is by far the most commercial readily available antimicrobial nanomaterial that has been used as a coating/additive (FeelFresh®, Silvadue™, Shieldex®) in many biomedical and healthcare products. Other nanomaterials such as Copper and Zinc are also gradually becoming more commercially ready as antimicrobial agents. However, recently, nanoparticle combinations, such as metallic alloy, composites, bimetallic and intermetallic materials (e.g., Ag-CuO, Ag-ZnO), have been found to have more pronounced and synergistic antimicrobial effects. [17,18]. Unfortunately, the antimicrobial data of nanoparticle combinations are not as readily available as the standard alone nanomaterials (i.e., Ag, Cu, CuO). Thus, this article aims to promote the potential and diverse applications of antimicrobial nanoparticles (AMNPs) in biomedical/healthcare sectors by means of combating AMR and preventing infectious disease transmission.

2. Nanomaterials

The intrinsic properties of nanoparticles, such as their size, shape, and capping conditions, play important roles in determining antimicrobial activities. Typically, the antimicrobial efficiency of nanoparticles increases with a decrease in size. This is due to the larger specific surface areas available in nanoparticles, which provide more active atomic surfaces and a higher chance of microbial exposures [19–21]. In theory, smaller size particles with the correct surface charge penetrate bacterial cells more easily. The generation of reactive oxygen species (ROS), which is one of the possible routes to antimicrobial mechanisms, has also been found to be size-dependent, with smaller nanoparticles inducing a higher level of ROS when interacting with microbial cells [15]. As there is a clear trend to a high demand in nanoparticle product and that the antimicrobial effects appeared to be greatly dependent on the size and shape of the nanoparticles, this paper reviewed the available methods for obtaining AMNP in various forms.

2.1. Nanoparticle Synthesis and Processing Methods

Currently, two main approaches are used to synthesise nanoparticles, the 'bottom up' approach and the 'top down' approach. Like natural biological systems, the bottom-up approach refers to when materials are built from atoms or molecules and are assembled into conformation. Products generated from this approach are usually smaller in size and more cost-effective. The top-down approach refers to the production of nanoparticles by breaking down bulk materials into the particles that are within the nanoscale size [22,23].

2.1.1. Bottom Up

Within the bottom-up approach, the synthesis of nanoparticles can be classified into the following categories:

1. Gas-phase synthesis: This is when nanoparticles are generated through the interaction of gaseous precursor components over a catalyst or prepared surface. For instance, chemical vapour deposition (CVD) is a method involving the deposition of a thin film of gaseous reactants onto a substrate. A thin film of product is generated on the substrate surface when it is heated at ambient temperature by combining gas molecules [24]. The advantages of CVD are in producing highly pure, uniform, hard and strong nanoparticles. However, CVD requires special equipment, and the gaseous by-products can be toxic [25]. Still, CVD is a widely used technique to deposit metallic nano silver layers on the substrate surface heated to the temperature

573 K at atmospheric pressure. Nano metal layers generated using this method were proved to be active against a wide spectrum of bacterial strains [26]. For example, the antimicrobial property studies of AgNPs and CuNPs deposited on the surface of such biomedical materials, such as titanium, TiAlNb alloy and steel (317 L), confirmed the inhibitory effect against *S. aureus* [27]. Spange et al. reported wound dressings that were functionalised with Ag NPs using the CVD technique were found to exhibit a strong antibacterial effect against both *S. aureus* and *Klebsiella pneumoniae* strains with a low concentration of the silver coating [28].

2. Liquid-phase synthesis: Two common processes are used to synthesise nanomaterials via liquid-phase synthesis; they are the 'sol-gel' and 'microwave assist' methods. Nanomaterials are formed via the sol-gel process. Although often limited to producing metal oxides (i.e., ZnO, TiO_2), it is sometimes preferred over using the gas-phase synthesis due to its simplicity and lower processing temperature required to produce nanoparticles at a higher rate [29]. Sol-gel synthesis typically uses metal alkoxides as the precursors or any other reactants that would form a homogeneous medium with the applied solvent. The process first undergoes hydrolysis/polycondensation reactions to form a colloidal suspension ('sol'). This is then followed by complete solvent evaporation (or calcination) to allow nano products to be formed via precipitation/recrystallisation. By controlling the parameters and drying conditions during the precipitation process, different forms of Nano products, such as gel-film, uniform particle coat, or nano-fibre, can be manufactured using this method. Nanopowder (i.e., iron oxide Fe_3O_4) can also be obtained using the sol-gel method by simply filtering the precipitated colloidal products [30,31]. Ismail et al. reported how raising the calcination temperature influenced the sizes and agglomeration in the ZnO NPs that were formed using the sol-gel process [32]. Khan et al. claimed to have used the sol-gel method to produce thorn-like ZnO nanoparticles, which showed good antimicrobial and antifungal activities against *Bacillus subtilis*, *Escherichia coli* and *Candida albicans* [33]. Research data suggest there has been an increased interest in utilising microwave radiation for nanoparticle synthesis. The electromagnetic energy produced by microwave power enables localised heating to be delivered to the reaction media. [34–37]. For instance, Yu S-H. and co-workers synthesised environment-friendly Ag NPs using a microwave reactor, where Silver nitrate ($AgNO_3$) was heated and irradiated in water at 150 °C whilst L-Lysine/L-arginine was respectively added as reducing agents and surfactants [38]. This reaction produced uniform and monodispersed Ag NPs with average particle sizes between 26.3 and 26.7 nm in diameter in ten seconds. The manipulation of microwave power and radiation time can also control the morphology of nanoparticles produced. Hasanpoor et al. found that microwave-assisted synthesis can produce needle-like nanoparticles, but when the microwave power was increased, the morphology changed into flower-shaped nanoparticles [36].
3. Biological synthesis: Biosynthetic methods can be divided into two classes, the mycosynthesis (utility of fungi) and phytonanotechnology (utility of plants) [39,40]. These eco-friendly methods are also known to produce nanoparticles with active biological function (i.e., antimicrobial). This way, Nanoparticles can be synthesised without utilising toxic chemicals or concerns over generations of harmful by-products. For instance, it is possible to replace the reducing agent used in chemical methods with harmless microorganisms or plant extracts [40]. Well-established biosynthetic methods for NP preparations can also be very cost-effective [41]. The production of antimicrobial Ag NPs via mycosynthesis was reported by Madakka et al., where fungi *Aspergillus niger* and *Fusarium semitectum* were utilised [42]. Although there are numerous advantages of using biological methods for nanoparticle synthesis, there are a few drawbacks. First, many of the mechanisms involved in these biosynthetic processes remain unclear. Second, it is not easy to manipulate the constituents in microorganisms or plant extracts to optimise the quality and quantity of nanomaterial

productions. Hence, nanoparticles formed using such synthetic methods often result in low production rates and yields.

2.1.2. Top-down

On the other hand, the top-down approach involves more mechanical and physical techniques, such as mechanical milling. The size of particles is decomposed by milling from the micro dimensions to the nanoscale with strong mechanical shear forces and post-annealing in an inert atmosphere [43]. The main problem of this method is the contamination of the nanomaterial from milling media and/or the atmosphere and powder consolidation, especially for highly energetic mills. For instance, continuous grinding using high-energy shaker mills can cause more than 10% Fe contamination from steel balls and containers [43]. Furthermore, if milling is to be carried out under atmospheric pressure, air (i.e., N_2 and O_2) can easily react with the milling media, such as metallic Al, Ti, Zr [43,44]. Hence, there are limitations to the type of nanomaterials that can be manufactured using this method.

Spray pyrolysis is alternatively used in industry for largescale production of nanoparticles, and such method involves burning a bulk precursor in either liquid or vapour form at high pressure and/or temperature, where the precursor is fed into the furnace through a hole or opening [45]. Some of the furnaces use laser and plasma instead of flame to deliver the energy that is required to perform complete evaporation of small micrometre-sized particles [46]. The advantages of using pyrolysis are that apparatus set-up can be quite simple, the production process can be very efficient and cost-effective, nanomaterials can be manufactured under a continuous process with high production yield. Ren et al. evaluated the physical and antimicrobial properties of Copper oxide nanoparticles (CuO NPs) that were engineered using the Tesima™ plasma process, as shown in Figure 2 [47]. TEM demonstrated particle sizes of CuO NPs generated using this method were in the range of 20 to 95 nm. These CuO NPs were also shown to inhibit a range of pathogenic bacteria (i.e., MRSA and *E. coli*). Although these techniques can be properly established for large-scale manufacturing processes, it does require large energy consumption and an intensive cleaning protocol in order to produce the desired materials in a highly pure state. It was also reported that materials produced using such an approach were more likely to agglomerate and be susceptible to surface contamination [23,48].

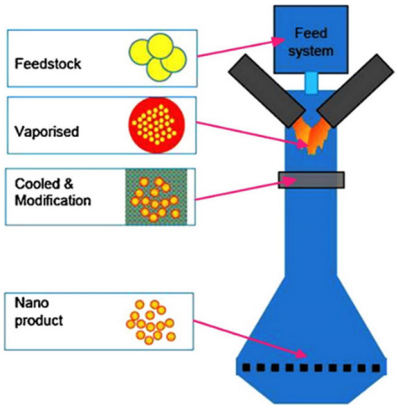

Figure 2. Schematic diagram of Tesima™ plasma process. Reproduced with permission from Ren et al., *International Journal of Antimicrobial Agents*; published by Elsevier, 2009. [47].

Once the desired nanopowder is produced, it can be treated and further processed into different forms to fit application purposes. Nanopowder can be dispersed into colloidal suspensions in different surfactants for coating/impregnating solid substrates to produce antimicrobial functions. They can be formulated into air-stable aerosols; Ag NPs containing aerosols are currently marketed as surface disinfectants, deodorisers, etc. [49]. Nanomaterials can also be formulated into an emulsion for pharmaceutical applications. For example,

sunscreens containing TiO_2 and ZnO nanoparticles are one of the most common emulsions with effectively protect skin by broadband ultraviolet (UV) radiation, whilst the application on the skin remains transparent [50].

2.2. Intrinsic Properties and Characteristics of Nanoparticles

Nanomaterials have been increasingly studied because of their unique physical, chemical, optical, magnetic and electrical properties in comparison to traditional bulk materials [1]. The two primary factors which provide nanomaterials with their unique properties include surface effect and quantum confinement effect [51]. Nanomaterials have a much greater surface area to volume ratio than their conventional forms. Compared to bulk materials, a large portion of the atoms reside on the surface than those in the core of the particle, and they are also found to be less stable (hence more reactive) due to lower coordination and the presence of unsatisfied bonds in their atomic structures [52]. In particular, where edge and corner atoms are often associated with the minimum energy interactions and binding with foreign atoms [51].

The Quantum confinement effect is associated with the discrete energy levels present in the atomic structure. In other words, when the particle sizes decrease to their nanoscale, the percentage of atoms on the surface increases, resulting in amplified activities and many special properties [51,53]. These factors affect the chemical reactivity of materials as well as leading to unique physical, chemical, optical, electrical and magnetic behaviours. As an example, it was reported that silver Ag NP with average-sized 3.5 nm have a melting temperature of approximately 112 °C, which is much lower in comparison to the corresponding bulk Ag (960 °C) [54]. Similarly, the melting point of the nano Cu (47 nm) was reported to be 670 °C lower than its equivalent bulk sample [55]. Furthermore, Zinc Oxide nanoparticles (ZnO NP) have also been widely studied due to their unique catalytic activities in chemical reactions and diverse organic syntheses [56,57].

Certain nanomaterials, such as gold (Au) and silver (Ag), are known to own unique optical properties called the Surface Plasmon Resonance (SPR), which is an oscillation of conductive electrons that resonate on the metal surface when it is being excited by a specific wavelength of light. The phenomenon and incidences of SPR found in nanomaterials have been receiving tremendous interest in biomedical research in the last decade [58–60]. The tuneable optical properties of noble nanoparticles (especially Au NPs) are highly dependent on their particle size and shape. Ag NPs with a diameter of 70 nm are known to scatter green light (~ λ_{max} 530 nm) and transmit to orange. However, when Nano gold (Au NPs) are added, the absorption band of Ag-Au alloy NPs shifts to longer wavelengths [61]. The first and very successful human clinical trial that involved the utility of Gold nano shells was performed in 2019 in photothermal cancer therapy. Gold nano shells were injected intravenously under human skin, irradiated by a near-infrared source and converted into heat energy, inducing highly localized hyperthermia (a photothermal reaction) and resulting in highly effective cell death and tumour remission [62]. This breakthrough has proven the safe administration of certain nanomaterials, the extended life expectancy of the patients who underwent this clinical trial and promoted a big step in utilising nanomaterials for biomedical and healthcare applications. It is worth noting that the same concept has already been intensively studied using Gold nanorods and triangular AgNPs in photothermal treatment for wound infection caused by *P. aeruginosa* and resistant bacteria in mice [58,63].

Similar to the melting, catalytic and optical properties, the antimicrobial activity of nanoparticles is influenced by their size-related physical behaviours. Although smaller nanoparticles have shown an increase in antimicrobial activity, smaller nanoparticles have also shown to have increased cytotoxic effects on mammalian cells. For example, Ag NPs at 10 nm produced more antimicrobial activity towards *Methylobacterium spp.* than Ag NPs at 100 nm; however, an increase in cytotoxicity was also seen towards human peripheral blood mononuclear cells [19]. As biological processes happen on the nanoscale, nanomaterials

with unique properties, as mentioned above, are expected to have great potential in biomedical applications by appropriately involving them in these processes [64].

2.3. Nanomaterials with Antimicrobial Properties

Although it was not claimed until the 19th century due to the absence of appropriate characterisation techniques, nano silver in colloidal form has actually been used as a biocidal material for more than 100 years [3]. The first Ag NPs colloid synthesis with particle sizes of 7–9 nm was reported by Lea, M.C. in 1889, who claimed to have stabilized such nanoparticles in citrate medium [65]. For the same reason as previously mentioned, the physical and chemical characterisations of these Ag NPs were not fully elucidated until 1969 [66], and the synthetic method was not recognised until 2009 [67]. As noted in the previous content and shown in Figure 1, due to the introduction of the antibiotic Penicillin in 1940, AMNP was not a popular area in research until the realisation and the rise in antibiotic resistance [68,69]. AMNPs consist of a range of materials; they may comprise a single element, a mixture of two or more elements, e.g., metal oxides, the combination of a metal element and oxygen. Furthermore, intermetallic and alloys are compounds composed of a combination of two or more metals or another element bonded together to form a defined stoichiometry structure [70,71].

2.3.1. Mono-Metallic Nanoparticles

Antibacterial metal has a long history. Ag NPs have been recently applied in various fields, such as dentistry, pharmaceutical and biomedical industries, due to their low toxicity and high antimicrobial efficacies [72]. It has been reported that Ag NPs with an average diameter of 21 nm and concentration of > 75 μg/mL inhibit a wide range of Gram-negative bacteria species (i.e., *Escherichia coli*, *Vibrio cholerae*, *Salmonella typhi* and *Pseudomonas aeruginosa*) [73]. The authors hypothesised possible mechanisms of such bacterial inhibition involve. First, Ag NPs disrupting cellular metabolic activity and inflicting membrane damage to the cells, which both subsequently trigger the generation of ROS and DNA damage [74]. In addition, according to other reports, Ag NPs can also induce pits and gaps in the bacterial membrane, which assist the further accumulation of Ag NPs and form free radicals causing cell death [75]. The release of Ag^{+}/Ag^{2+} ions is also considered as the main bactericidal mechanism, which interact with disulphide or sulphydryl groups of enzymes, leading to disruption of cellular metabolic processes [76,77].

In another study, Ag NPs with a 12.4 nm diameter were found to reduce bacterial growth on agar plates and at concentrations of 10–100 μg/mL were required to act against *E. coli* at 10^5 colony forming units (CFUs) [75]. As expected, increased concentrations of Ag NPs, increased inhibitory effects on bacteria. For instance, at a concentration of 10 μg/mL, the Ag NPs only inhibited 70% CFU of the *E. coli* populations, whereas increasing the NPs concentration to 50 μg/mL or above completely inhibited *E. coli* growth. In microbiology, the minimum inhibitory concentration (MIC) is defined as the lowest concentration of nanoparticles that inhibits the growth of a microorganism, and it is a method that is commonly used to assess the susceptibility of microorganisms to antimicrobials. Ag NPs solutions that were synthesised in situ via the reduction of silver nitrate showed to have directly inhibited the growth of bacteria. It was found that the MIC_{50} of Ag NPs against *E. coli* was estimated to be between 3.3 nM and 6.6 nM, whilst MIC_{100} was achieved at the concentration of 33 nM. In the case of Gram-positive species, *S. aureus*, MIC_{100} was not detected as it appeared the required concentration to be well beyond the raw concentration of the synthesised materials [78]. In a separate experiment, Pal et al. investigated how antibacterial activities relate to the shape of Ag NPs [79]. They found that triangular nanoparticles with an average edge length of 40 nm displayed the strongest bactericidal activity, reducing *E. coli* viability more extensively when compared to spherical (mean sizes = 39 nm) and rod-shaped (mean sizes = 133 × 16 nm) Ag NPs. These triangular-shaped Ag NPs predominated, with a {111} surface, with high-atom-density facets, and they were found to contain saturated Ag^{+}/Ag^{2+} ions. The bacterial colony was completely

inhibited by 1 μg of triangular Ag NPs, whilst more than 12.5–50 μg of spherical-shaped nanoparticles were required to inhibit the bacterial growth significantly. In contrast, 100 μg of rod-shaped nanoparticles and $AgNO_3$ were unable to achieve the same effect.

Another study concerning the size- and shape-dependent antimicrobial activity proposed the smaller size of Ag NPs proved the better performance of antimicrobial against Gram-positive (*Staphylococcus epidermidis* and *Bacillus megaterium)* and Gram-negative bacteria (*P. aeruginosa*). The authors concluded Ag NPs are potentially applicable in clinical wound dressing, bio-adhesives, biofilms and the coating of biomedical materials [80]. Moreover, certain Ag NPs have been found to inhibit activity against antibiotic-resistant species also. For example, Lara et al. found Ag NPs of 100 nm had antimicrobial activity against erythromycin-resistant *S. pyogenes*, ampicillin-resistant *E. coli* 0157:H7 and multidrug-resistant *P. aeruginosa.* On average, the MIC was found to be 79.4 nM, which was slightly higher than the MIC for drug-susceptible species (71.5 nM) [81]. Similarly, Singh et al. found Ag NPs derived from *Phyllanthus amarus* were antimicrobially effective against multidrug-resistant *P. aeruginosa*, with MIC values of 6.25–12.5μg/mL, which are comparable to antibiotic concentrations towards the susceptible strains. [82]

Despite Cu being an essential trace element in most organisms, excessive concentrations of exogenous Cu can be toxic [83]. In addition, Cu NPs have a lower economic cost and are known to have a wider microbial inhibition range than Ag NPs [84,85]. Although, in some cases, higher Cu NPs concentrations were required to inhibit the target microbes, whereas when the same Ag NPs concentration was employed, it would show zero inhibitory effect [85]. A good example can be seen in Bankier's study. No inhibitory effect was observed when 0.25 w/v% of Ag NPs was incubated with *S. aureus*, whilst at the same Cu NPs concentration, >99.5% microbial reduction was detected. Currently, three widely recognized antimicrobial mechanisms of Cu have been proposed amongst other numerous and complex mechanisms. First, the redox activity of the Cu (as well as Fe and Zn) ion catalysise the Haber–Weiss and Fenton reactions by shuttling between cupric ions (Cu^{2+}) and cuprous ions (Cu^{+}):

$$Cu^{+} + H_2O_2 + O_2^{-} \rightarrow O_2 + Cu^{2+} + OH^{-} + \bullet OH \text{ (Haber} - \text{Weiss reaction)}$$

$$Cu^{+} + H_2O_2 \rightarrow Cu^{2+} + OH^{-} + \bullet OH \text{ (Fenton reaction)}$$

In such a reaction, ROS and hydroxyl free radicals are formed, which can damage a range of cellular molecules, causing mutations in DNA [86]. In addition, Cu^{+}/Cu^{2+} ions can easily combine with sulphur-, nitrogen- or oxygen-containing functional groups to form organometallic complexes, resulting in defects in the conformational structure of nucleic acids and proteins [84]. Lastly, Cu^{+}/Cu^{2+} ions may also compete with non-Cu metal ions for important binding sites on proteins leading to reduced cellular functions [83]. Taking the inhibition of *E. coli* as an example, excess Cu leads to a disintegration of iron–sulphur clusters, which are essential in dehydratase enzymes, leading to the inability of *E. coli* to biosynthesize amino acids [87].

A separate research demonstrated that Cu NPs suspensions with a particle size of 100 nm at concentrations 33.4 and 28.2 μg/mL, respectively, reduced 90% populations of *E. coli* and *B. subtilis*, whilst complete inhibitions of both bacteria were observed at doses over 60 μg/mL [88]. The MIC test was also carried out by placing nanoparticle-impregnated filter paper on agar plates. The MIC of Cu NPs for *E. coli* was 140–280 μg/mL, whilst that for *S. aureus* was 140 μg/mL [89]. In another study, Usman et al. stated Cu-chitosan nanoparticles with a size of 2 to 350 nm can inhibit microorganisms including *S. aureus, B. subtilis, P. aeruginosa, S. choleraesuis* and *Candida albicans* [90].

It is known that Cu NPs can easily undergo oxidation in the presence of air/water. However, their oxidised intermediate (Cuprous oxide Cu_2O) and product (Copper oxide CuO) are both known to possess antimicrobial activities that are effective against a range of pathogens, such as *Klebsiella pneumoniae, P. aeruginosa, S. paratyphi* and *Shigella* strains, in a similar way to Cu NPs [90]. For instance, Mahapatra et al. stated CuO NPs can cross

through the bacterial cell membrane and then damage the vital enzymes of bacteria to inhibit cells [91].

A study was performed by Ren et al., where ultra-fine CuO NPs (10 nm) were prepared using a patented thermal plasma technology (Figure 2). These CuO NPs were found to counteract various bacteria via in vitro MBC determination, along with other nanoparticles (i.e., Cu and Ag) that were engineered under the same conditions, along with other nanoparticles (i.e., Cu and Ag) that were engineered under the same conditions [47].

With regard to MIC, Ahamed et al. used a broth microdilution method with a 96-well microtiter plate technique to determine the antimicrobial activity of 23 nm CuO NPs against various bacterial strains [92]. They indicated that the lowest MIC of CuO NPs (31.25 µg/mL) was for *E. coli* and *E. faecalis*, whilst the highest MIC (250 µg/mL) was for *K. pneumonia*. In another similar research, Azam et al. confirmed that the inhibitory effects of CuO NPs relate to size, stability, and concentration by annealing at different temperatures. They also synthesised CuO NPs with a minimum size of 20 nm to achieve the MIC value of 20 ± 3 µg/mL for *E. coli*, which is lower than the previous result of 23 nm CuO NPs [21].

Antimicrobial research has shown a growing interest in Zinc Oxide (ZnO) due to its apparent toxicity to certain pathogens [93] and the recognition of its biocompatibility in biomedical applications [94]. Azam et al. stated ZnO NPs achieve the most effective bactericidal activity amongst CuO and Fe_2O_3 against Gram-negative (*E. coli and P. aeruginosa*) and Gram-positive (*S. aureus* and *B. subtilis*) bacteria [95]. As previously mentioned, redox reactions of Cu can lead to the generation of H_2O_2 and ROS, which can damage cellular molecules and cause mutations in DNA [86]. A number of research studies suggested that the antimicrobial mechanisms of ZnO NPs pose similar processes to Cu/CuO NPs, where the generation of Zn ions, H_2O_2 and ROS were involved in affecting microbial cells [96–99]. Other observed electrostatic binding and accumulation of the actual ZnO particles on the bacterial surface cause structural integrity damage to the cell walls [96].

Typically, ZnO NPs are found to be more effective than micron-sized ZnO particles. Micro- and nano-sized ZnO particles at a concentration of 20 µg/mL were used to inhibit *B. subtilis*, *E. coli* and *P. fluorescens*. ZnO in nano-size totally reduced all tested bacteria species, whilst micro-sized ZnO inhibited 50 to 100% of all tested bacteria species [100]. Furthermore, in another antimicrobial study using a standard microbial method, Padmavathy et al. prepared ZnO NPs with various particle sizes; the smallest size (12 nm) of ZnO exhibited the highest efficacy [101]. The authors explained the greater the number of nanopore particles, the higher the generation of active oxygen species, and thus they kill bacteria more effectively. They also proposed that both the abrasiveness and the surface oxygen species of ZnO NPs can promote the biocidal properties of ZnO NPs.

2.3.2. Nanoparticles Combinations with Synergistic Effects

With regards to the mixture of metallic nanoparticles, one of the major advantages is that they produce a higher antimicrobial effect combined compared to single elemental nanoparticles. Miguel et al. investigated the antimicrobial activities of six metal and metal oxide nanoparticles and two of their composites [102]. They found the mean MIC of ZnO and Ag-ZnO composites were, respectively, 437.5 and less than 362.5 µg/mL, whilst the mean MIC of CuO and Ag-CuO composites were, respectively, 312.5 and less than 237.5 µg/mL. Both MIC values of the Ag-ZnO and Ag-CuO were significantly lower than the parent materials. There are some advantages to using nanocomposites, such as minimising the utilities of precious and potentially toxic metallic ingredients, which in turn, reduces the cost and may potentially diminish bacterial resistance. Recent AMNP composites claiming to contain Cu, Ag and WC nanoparticles showed stable inhibitions (99.99%) against various deadly pathogens [8].

In other studies, intermetallic compounds have been studied as antimicrobial agents. Silver–Gold (Ag–Au) alloy nanoparticles combined with penicillin G and piperacillin intensified the antimicrobial effect against *S. aureus* [103]. The authors suggested that such

nanoparticles can potentially be used as an adjuvant in combination therapy of antibiotics. It is interesting to note that bimetallic NPs derived from noble Gold and Platinum (Au-Pt) were also found to produce antimicrobial activity against microbes, including multidrug-resistant *E. coli*. Certain bimetallic formulas have been shown to have MIC as low as 5 µg/mL and are still effective against resistant *E. coli* [104].

A group from China demonstrated the Ti-Ni-Cu shape memory alloys simultaneously possess excellent shape memory effects, cytocompatibility and antibacterial properties after adding a Cu alloying element [105]. The future application of this compound includes biomedical implants and devices with reduced bacterial infections. A recent work showed that the Pt-Ag nanoparticles remarkably enhanced multiple enzyme-mimicking activities related to oxygen reduction reactions and exerted excellent antibacterial effects on *E. coli* and *S. aureus* [106]. A forthcoming work relates the controllable synthesis of high-quality nanoalloys to their novel catalytic properties for various promising applications, including catalysts, biosensors and biomedicine. Lastly, Table 1 summarizes all mentioned nanoparticles that have been studied for antimicrobial effects.

Table 1. Summary of nanoparticles that have been tested for antimicrobial activity.

Monometallic/Metal Oxide Nanoparticles	Mean Size (Shape)	Bacteria/Fungi Tested	Reference
Silver (Ag)	21 nm (cuboctahedron icosahedron and decahedron)	*E. coli* *V. cholerae* *S. Typhi* *P. aeruginosa*	[73]
	12.4 nm	*E. coli* *Yeast*	[75]
	13.5 nm (spherical)	*E. coli* *S. aureus*	[78]
	39 nm (spherical); 16 nm (rod)	*E. coli*	[79]
	1.5–10 nm (spherical, triangular and polyhedron)	*S. epidermidis* *B. megaterium* *P. aeruginosa* *E. coli* *C. albicans* *A. niger*	[80]
Copper (Cu)	100 nm (spherical)	*E. coli* *B. subtilis*	[88]
	9 nm (quasi-sphere)	*E. coli* *S. aureus*	[89]
	2–350 nm	*S. aureus* *B. subtilis* *P. aeruginosa* *S. choleraesuis*	[90]
	80–160 nm	*C. albicans* *K. pneumoniae* *P. aeruginosa* *S. paratyphi* *Shigella*	[91]
Copper oxide (CuO)	20–95 nm (rod and rectangle)	EMRSA MRSA *S. aureus* *S. sepidermidis* *E. coli* *Proteus spp.* *P. aeruginosa*	[47]

Table 1. *Cont.*

Monometallic/Metal Oxide Nanoparticles	Mean Size (Shape)	Bacteria/Fungi Tested	Reference
	23 nm	*E. coli* *E. faecalis* *K. pneumonia*	[92]
	20–28.9 nm	*E. coli* *P. aeruginosa* *B. subtilis* *S. aureus*	[21]
Zinc oxide (ZnO)	20 nm	*E. coli* *P. aeruginosa* *S. aureus* *B. subtilis*	[95]
	20 nm	*B. subtilis* *E. coli* *P. fluorescens*	[100]
	20–40 nm	*E. coli*	[101]
Intermetallic Nanoparticles	**Mean Size (nm)**	**Bacteria/Fungi Tested**	**Reference**
Silver-Gold alloy (Ag-Au)	<200 nm (spherical)	*S. aureus*	[103]
Titanium-Nickel-Copper alloy (Ti-Ni-Cu)	N/A	*S. aureus* *E. coli*	[105]
Platinum-Silver alloy (Pt-Ag)	N/A	*E. coli* *S. aureus*	[106]

3. Mechanisms of Action of Antibiotics and Nanoparticles Against Bacteria

3.1. Gram-Negative and Gram-Positive Bacteria

Most bacteria can be divided into two separate classifications based on their cell wall structure: Gram-positive and Gram-negative. Figure 3 shows a schematic diagram of the differences between Gram-negative and Gram-positive bacterial cell wall structures. The cell wall of a typical Gram-negative bacterium, such as *E. coli* and *P. aeruginosa*, is made up of an inner membrane, a thin peptidoglycan layer, with an additional outer membrane consisting of lipopolysaccharides and phospholipids, whilst the major layers of Gram-positive bacteria cell wall are slightly different—a thick peptidoglycan layer, containing teichoic acids. Overall, bacteria sizes vary from 0.5 µm to 5 µm in diameter [107].

3.2. Antibiotic-Resistant Mechanisms in Microorganisms

Antibiotics are prescribed to treat and prevent bacterial/fungal infections. Antibiotics target certain pathways, such as cell wall synthesis, to produce a mechanism of action against microorganisms [108]. However, microorganisms can prevent the accumulation of antibiotics, which reduces and resists the antimicrobial effects. There are currently three main mechanisms of resistance: (1) mutations in the microorganism's outer membrane to allow a decrease in antibiotic uptake or an increase in efflux of antibiotic from the cells; for instance, due to the presence of an outer bacterial membrane, Gram-negative bacteria are more likely to be resistance to antibiotics as they have to penetrate through the protective barrier; (2) change in the target site where the antibiotic attaches to the microorganism (commonly due to spontaneous mutation) thus reducing the sensitivity to the antibiotic and (3) the production of inactivating enzymes [108–111].

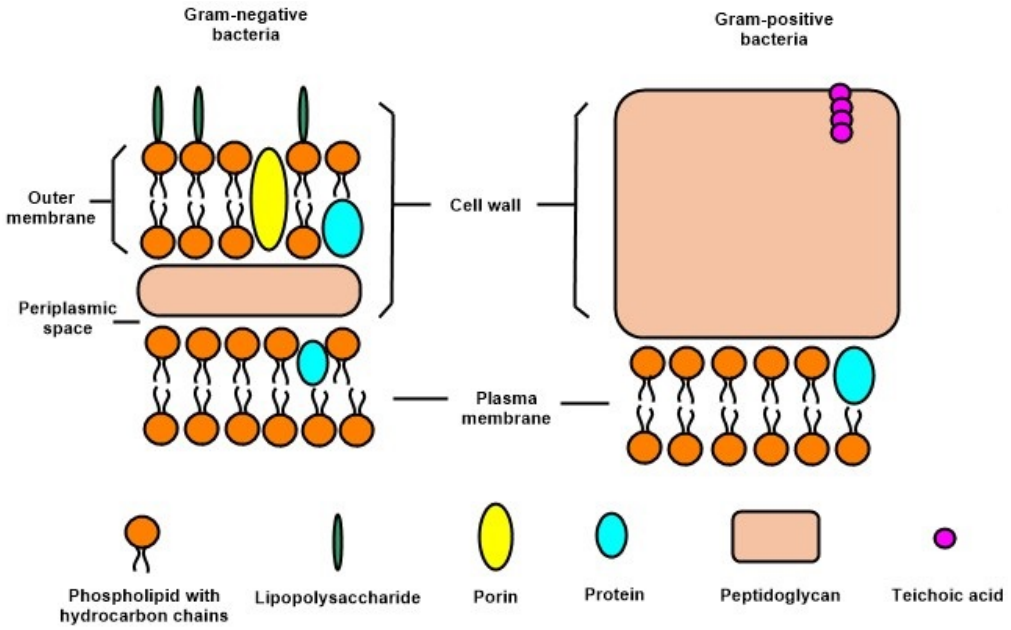

Figure 3. Structure difference of Gram-negative and -positive bacteria. Reproduced with modification from Slavin et al., *Journal of Nanobiotechnology*; published by Spring Nature, 2017. [15].

Not only do these resistant species pose a threat through ineffective antibiotic treatment, but the resistant species can also pass on resistance genes to other microbes. Resistant genes can be found encoded in gene cassettes located within the transposon and the chromosomes of microbes [112,113]. Through horizontal gene transfer, these gene cassettes can be transferred to another microbe. Currently, there are three main mechanisms of horizontal gene transfer: conjugation (transfer of genetic material through direct contact between cells with resistance and receptor cells), transformation (uptake and incorporation of short resistant DNA into receptor microbe) and transduction (transfer of resistant DNA to receptor microbe via bacteriophage vector) [114].

3.3. The Mechanisms of Actions of Antimicrobial Nanoparticles

In general, four proposed theories were considered to trigger the bactericidal deactivations, depending on the chemistry (i.e., constituents/ionic states) and the physical properties (i.e., particle shapes/sizes) of the nanoparticles. Figure 4 shows a representative diagram of the four possible mechanisms, and their details can be explained as follow:

1. Reactive oxygen species (ROS): ROS include superoxide anion (O_2^-), hydroxyl radicals ($\bullet OH$) singlet oxygen (O_2) and hydrogen peroxide (H_2O_2) (by-products of cellular oxidative metabolism) [115]. Typically, redox-active essential metals present in biomolecules act as catalytic cofactors when ROS are either generated or catalysed by cell enzymes. The presence of external metals intensifies reactions producing an excess of ROS that trigger oxidative stress and subsequently lead to cellular programmed death [116,117]. With specific metals, an occurrence of Fenton reactions both increases the formation of ROS and stimulates the electron transport chain to eventually promote bacteria death through the catabolism of the carbon source and the generation of nicotinamide adenine dinucleotide [13].
2. Dissolved metal ions: external metal ions are absorbed through the cell membrane and inhibit cellular function or enzyme activity by interacting with the functional groups of proteins and nucleic acids, which eventually affect the normal physiological processes [14].
3. Physical interaction: unlike antibiotics, Gram-negative bacteria are more vulnerable to nanoparticle mechanisms of action since their wall structure may assist released ions from the nanoparticle into the cell. In addition, although both bacteria cell walls

are dominated by negative charges, Gram-negative bacteria have a higher affinity for the positive ions due to electrostatic attraction [15].

4. Internalisation into the cell: smaller sizes of particles are likely to enter the cells via endocytosis. Subsequent, released nanoparticle ions are then up-taken in high intracellular concentration, which leads to oxidative stress [16].

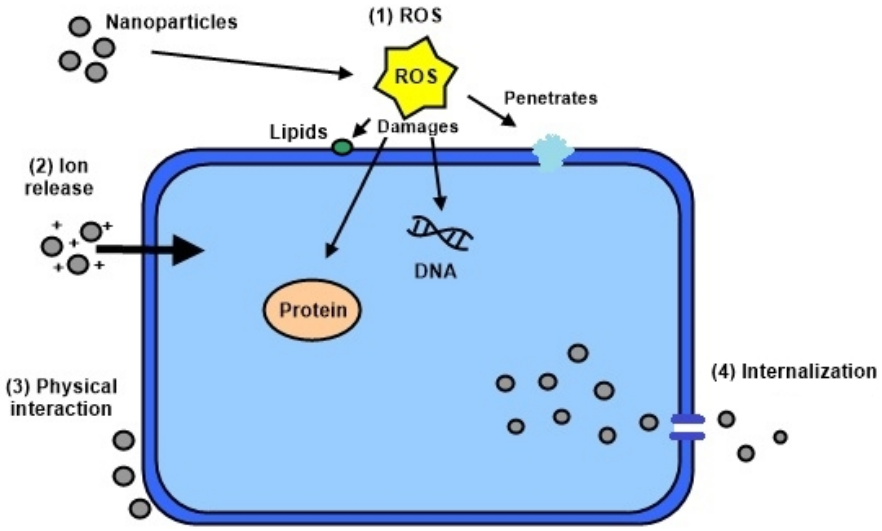

Figure 4. Various antimicrobial activities of metal nanoparticles. Reproduced with modification from Dizaj et al., *Materials Science and Engineering*: C; published by Elsevier, 2014. [72].

It is known that smaller-sized nanoparticles enhance antimicrobial properties due to the increase in surface area to volume ratio. Conversely, smaller-sized particles have shown an increase in toxicity towards mammalian cells; thus, concentration and leaching of nanoparticles from products are also to be considered [19,118]. Moreover, common physiochemical behaviour, such as particle agglomerations that were found in nanoparticles when suspended in a biological medium, appeared to reduce antimicrobial effectiveness [119].

4. Applications of Antimicrobial Nanoparticles

As mentioned, although the term nanoparticle has only been recognised in the 19th century, it indeed has a long ancient history of medical applications. Under the name "Collargol", "Argyrol" and "Protargol", although the physiochemistry of such Ag NPs were not determined until the 19th century [120], these commercial products have been manufactured since 1897 and have been used by medical doctors to treat various diseases, such as syphilis and other bacterial infections [3,121]. Moreover, for many decades, nano silver, formerly known as colloidal silver, has also been used as additives for wound care, water filtration systems, algicides and disinfectants (e.g., trade names Silver Algaedyn, Nu-Clo Silvercide, ASAP-AGX).

With the attractive properties and fruitful diversity found in nanoparticles, there has been an increasing trend of manufactured products that involved the utilities of such antimicrobial nanoparticles for a wide range of healthcare applications. In particular, BASF and Evonik Degussa are the biggest markets that offer nanomaterials in cosmetics and personal hygiene [122]. It was estimated in 2016 that the global market for nanomaterials was between 300,000 to 1.6 million tons. Amongst all, Ag NPs are one of the most common nanoparticles utilised in healthcare applications; about 135–420 tons of Ag NPs were produced in 2014, with the Asian region accounting for the largest market share. Needless to say, along with commercial applications of antimicrobial Ag NPs products, the research and development of other NPs and their utilities in healthcare applications are also rapidly growing.

4.1. Fabrics and Fibres

Textile fibres have been incorporated with nanoparticles to produce clothing and shoe pads with special properties [123]. The addition of antimicrobial nanoparticles is primarily used to exploit their antimicrobial properties to decrease odour-producing bacteria and fungi, but recent studies have investigated applications to reduce bacterial contamination that may cause disease [124–127]. Studies have shown a variety of ways to produce nanoparticle incorporated fibres, with Ag as the common antimicrobial nanoparticle. A study by Yeo et al. suggested two types of spun fibres containing Ag NPs in sheath-part with, respectively, 0.3 and 1.5 wt% inhibited 99.9% of *E. coli* and *K. pneumoniae* [128]. In another study, Gerber et al. prepared Ag-tricalcium phosphate nanoparticles using flame spray synthesis and generated polyamide fibres incorporated with the nanoparticles through the process of extrusion and melt-spun fibres [129]. The polymer fibres were able to effectively reduce 99.999% of *E. coli* and 99.6% of *S. sanguinis* within 24 h. In another case, Zhang et al. immersed cotton fabrics with chitosan and $AgNO_3$ nanoparticle solutions to produced cotton fabrics with Ag NPs. The fabrics were able to inhibit *E. coli* and had less fabric colour change after 81 washes [130]. Lastly, pressurised gyration was used by Illangakoon et al. to produce nanoparticle (including Cu, Ag and W) embedded polymer fibres with the potential antimicrobial applications for water and air filter systems. These filters had shown successful inhibition of *P. aeruginosa* (over 70% reduction). The SEM images of these antimicrobial filter mats are shown in Figure 5 [11].

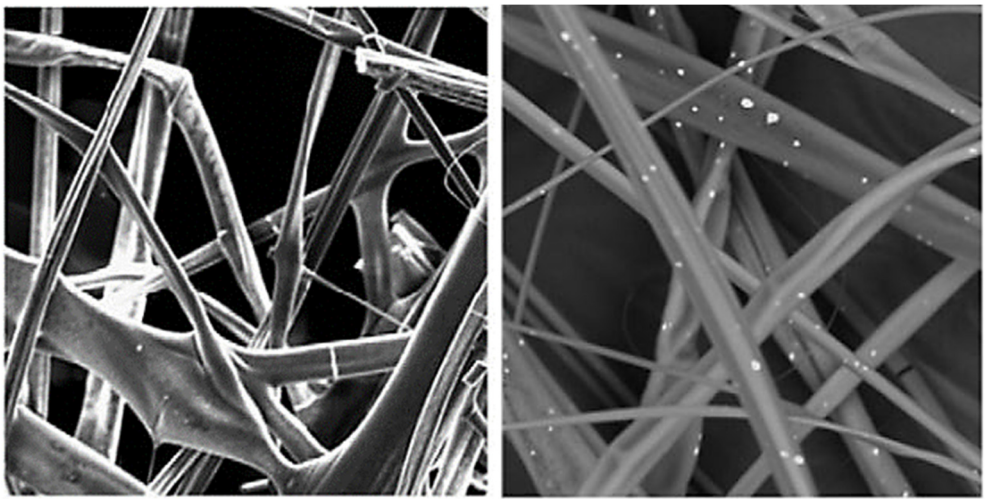

Figure 5. SEM images of PMMA fibre before (**left**) and after antimicrobial nanoparticles embedded into fibre mats (**right**). Reproduced with permission from Illangakoon et al., *Materials Science and Engineering C*; published by Elsevier, 2017. [11].

Although all the produced nanoparticle incorporated fabrics and fibres mentioned have shown effective antimicrobial activity, the examples are based on research studies and are not marketed currently.

4.2. Surface Films and Coating

One of the most well-known applications of antimicrobial nanomaterials is the use of Ag NPs on the surfaces of objects, such as laptops and keyboards [131]. Recently, Corning® produced an antimicrobial glass for electronic mobile devices. Corning® Gorilla® Glass 3 is a scratch-resistant glass incorporating Ag to produce an antimicrobial effect. Muzslay et al. reported that the glass was effective at reducing MRSA and *K. pneumonia* contamination [132].

In 2016, diarrhoeal disease was the ninth highest cause of death globally (WHO). The primary cause of diarrhoea is usually through the consumption of food or water that is contaminated with bacteria, including pathogenic strains of *E. coli* [133]. Since then, to control

contamination and to extend the life of fresh vegetables, fruit juice and meat, AMNPs are incorporated into prototype food packaging but still require studying to understand leaching and the effects of nanoparticle consumption. Ahmed et al. used a compression moulding technique to produce plasticized polylactide composite films containing bimetallic Ag-Cu nanoparticles and cinnamon essential oils. The film was found to have antibacterial activity against common pathogens found on chicken meat [134]. Similarly, to produce low-density polyethylene (LDPE) films with Ag and ZnO, Emamifar et al. mixed nanoparticle powders with LDPE resin pellets in a twin-screw extruder machine, and a single screw blowing machine was used to produce a 50 µm thick nanocomposite film. Antimicrobial activity tests against *L. plantarum* were done and showed that nano Ag films were more effective than nano zinc oxide films [135]. Lastly, An et al. generated an Ag NP polymer-based coating for vegetables by adding $AgNO_3$ to polyvinylpyrrolidone, followed by glycerol. Asparagus spears were immersed in the coating, and it was found to prolong their life when evaluating the firmness, weight loss and colour [136].

4.3. Healthcare Applications

Contaminated surfaces are one of the leading causes of hospital infection transmission; some bacteria and fungi can survive for up to four months on inanimate surfaces [137,138]. Paints have been treated with nanoparticles to produce an antimicrobial coating finish that protects and prevents surfaces from supporting bacterial or fungi growth to reduce pathogen contamination on surfaces. Oil-based antimicrobial paints are increasingly used in hospitals to provide a reduced pathogenic environment on wooden, glass and polystyrene surfaces [139]. Equally, antimicrobial polymer coating has been developed to protect devices made from stainless steel, glass or polyvinyl fluoride. However, studies have shown that AMNP containing paints and coating are not effective against all types of bacteria [140]. In addition, the physical properties of antimicrobial paint may not be suitable for hospital settings. For example, NanoCote (commercialised antimicrobial paint with Cu NPs) was investigated by Ramsden et al., who found that the paint coating resulted in a slippery surface, colour loss after water contact and unattractive appearance [141].

Nanoparticles can be coated on medical sutures and implant devices. Zhang et al. investigated the effectiveness of sutures coated in silver nanoparticles and found that they produced antimicrobial activity against *E. coli* and had an anti-inflammatory effect [142]. Some medical implant devices have AMNP coating to reduce the risk of secondary infections and/or surgical complications. For example, TiO_2 nanoparticle coating on heart valve implants is used to inhibit Streptococcus species and *E. coli* [143,144]. Other types of implants made with nanoparticles include Ag incorporated polymer catheters [145,146]. Furthermore, Yassin et al. coated polymers of urinary catheters with silver nanoparticles. This produced antimicrobial activity against both Gram-negative and Gram-positive bacteria, in addition to bacterial adherence and formation of biofilms on the surface of the catheter [147]. However, both examples are currently researched applications rather than commercialised products.

Lastly, wound dressing infused with nanoparticles has been reported to be particularly useful in decreasing the risk of infections in wounds and aiding the healing process. The current commercial dressing, Biatain® AG non-adhesive foam dressing, contains a Ag complex that is effective at inhibiting *S. aureus* and other bacteria [148,149]. The utilities of Ag NPs in both artificial implants and wound dressings have been developed with antimicrobial features to help reduce infections and inflammation caused by microbes and biofilm formation [150].

5. Concluding Remarks and Future Perspectives

This paper first reviewed the introduction and different synthetic methods of nanoparticles. Commonly known AMNPs, including mono- and multi-elemental metals, were then discussed, and their involvement in the potential antimicrobial mechanistic pathways was also considered. Different resistant mechanisms found in mutated pathogens were also

mentioned with an aim to raise the awareness of global issues over AMR and the abusive usage of antibiotics. Finally, commercially available and potential antimicrobial products with embedded nanoparticles were reviewed. These have provided an insight into the level of relaxation/restriction of using metallic nanoparticles for antimicrobial applications in different industries. Future perspectives should focus on optimizing antimicrobial efficacies and the synergistic antimicrobial potentials of these nanoparticles along with their potential adverse cytotoxic effects in different mammalian cells.

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References

1. Tolochko, N. History of nanotechnology. In *Nanoscience and Nanotechnology Encyclopaedia of Life Support Systems (EOLSS)*; Developed under the Auspices of the UNESCO; SEolss: Oxford, UK, 2009.
2. Harden, D.B.; Toynbee, J.M.C. VII.—The Rothschild Lycurgus Cup. *Archaeologia* **1959**, *97*, 179–212. [CrossRef]
3. Nowack, B.; Krug, H.F.; Height, M. 120 Years of Nanosilver History: Implications for Policy Makers. *Environ. Sci. Technol.* **2011**, *45*, 1177–1183. [CrossRef]
4. Sengupta, S.; Chattopadhyay, M.K.; Grossart, H.P. The mulitfaceted roles of antibiotics and antibiotic resistance in nature. *Front. Microbiol.* **2013**, *4*, 47. [CrossRef] [PubMed]
5. Piddock, L.J. The crisis of no new antibiotics–what is the way forward? *Lancet Infect. Dis.* **2012**, *12*, 249–253. [CrossRef]
6. Atlanta, G.; CDC. *Antibiotic Resistance Threats in the United States*; Call of Duty Control, Ed.; U.S. Department of Health and Human Services: Washington, DC, USA, 2019.
7. WHO. *Global Action Plan on Antimicrobial Resistance*; World Health Organization: Geneva, Switzerland, 2015.
8. Ren, G.; Oxford, J.S.; Reip, P.W.; Lambkin-Williams, R.; Mann, A. Anti-Viral formulations Nanomaterials and Nanoparticles. U.S. Patent 13/691,099, 18 April 2013.
9. Allaker, R.P.; Ren, G. Potential impact of nanotechnology on the control of infectious diseases. *Trans. R. Soc. Trop. Med. Hyg.* **2008**, *102*, 1–2. [CrossRef]
10. Bankier, C.; Cheong, Y.; Mahalingam, S.; Edirisinghe, M.; Ren, G.; Cloutman-Green, E.; Ciric, L. A comparison of methods to assess the antimicrobial activity of nanoparticle combinations on bacterial cells. *PLoS ONE* **2018**, *13*, e0192093. [CrossRef]
11. Illangakoon, U.E.; Mahalingam, S.; Wang, K.; Cheong, Y.-K.; Canales, E.; Ren, G.; Cloutman-Green, E.; Edirisinghe, M.; Ciric, L. Gyrospun antimicrobial nanoparticle loaded fibrous polymeric filters. *Mater. Sci. Eng. C* **2017**, *74*, 315–324. [CrossRef]
12. Prabhu, S.; Poulose, E.K. Silver nanoparticles: Mechanism of antimicrobial action, synthesis, medical applications, and toxicity effects. *Int. Nano Lett.* **2012**, *2*, 32. [CrossRef]
13. Webster, T.J.; Leuba, K.D.; Durmus, N.G.; Taylor, E.N. Short communication: Carboxylate functionalized superparamagnetic iron oxide nanoparticles (SPION) for the reduction of S. aureus growth post biofilm formation. *Int. J. Nanomed.* **2013**, *8*, 731. [CrossRef]
14. Grass, G.; Rensing, C.; Solioz, M. Metallic Copper as an Antimicrobial Surface. *Appl. Environ. Microbiol.* **2011**, *77*, 1541–1547. [CrossRef]
15. Slavin, Y.N.; Asnis, J.; Häfeli, U.O.; Bach, H. Metal nanoparticles: Understanding the mechanisms behind antibacterial activity. *J. Nanobiotechnol.* **2017**, *15*, 65. [CrossRef]
16. Lai, H.-Z.; Chen, W.-Y.; Wu, C.-Y.; Chen, Y.-C. Potent Antibacterial Nanoparticles for Pathogenic Bacteria. *ACS Appl. Mater. Interfaces* **2015**, *7*, 2046–2054. [CrossRef]
17. Cheong, Y.-K.; Arce, M.P.; Benito, A.; Chen, D.; Crisóstomo, N.L.; Kerai, L.V.; Rodríguez, G.; Valverde, J.L.; Vadalia, M.; Cerpa-Naranjo, A.; et al. Synergistic Antifungal Study of PEGylated Graphene Oxides and Copper Nanoparticles against Candida albicans. *Nanomaterials* **2020**, *10*, 819. [CrossRef] [PubMed]
18. Bankier, C.; Matharu, R.K.; Cheong, Y.K.; Ren, G.G.; Cloutman-Green, E.; Ciric, L. Synergistic Antibacterial Effects of Metallic Nanoparticle Combinations. *Sci. Rep.* **2019**, *9*, 16074. [CrossRef] [PubMed]

19. Jeong, Y.; Lim, D.W.; Choi, J. Assessment of Size-Dependent Antimicrobial and Cytotoxic Properties of Silver Nanoparticles. *Adv. Mater. Sci. Eng.* **2014**, *2014*, 1–6. [CrossRef]
20. Agnihotri, S.; Mukherji, S.; Mukherji, S. Size-controlled silver nanoparticles synthesized over the range 5–100 nm using the same protocol and their antibacterial efficacy. *RSC Adv.* **2014**, *4*, 3974–3983. [CrossRef]
21. Azam, A. Size-dependent antimicrobial properties of CuO nanoparticles against Gram-positive and -negative bacterial strains. *Int. J. Nanomed.* **2012**, *7*, 3527–3535. [CrossRef] [PubMed]
22. Sabatier, P.A. Top-Down and Bottom-Up Approaches to Implementation Research: A Critical Analysis and Suggested Synthesis. *J. Public Policy* **1986**, *6*, 21–48. [CrossRef]
23. Arole, V.M.; Munde, S.V. Fabrication of nanomaterials by top-down and bottom-up approaches—An overview. *JAAST Mater. Sci.* **2014**, *1*, 89–93.
24. Bhaviripudi, S.; Mile, E.; Steiner, S.A.; Zare, A.T.; Dresselhaus, M.S.; Belcher, A.M.; Kong, J. CVD Synthesis of Single-Walled Carbon Nanotubes from Gold Nanoparticle Catalysts. *J. Am. Chem. Soc.* **2007**, *129*, 1516–1517. [CrossRef] [PubMed]
25. Adachi, M.; Tsukui, S.; Okuyama, K. Nanoparticle Synthesis by Ionizing Source Gas in Chemical Vapor Deposition. *Jpn. J. Appl. Phys.* **2003**, *42*, L77. [CrossRef]
26. Piszczek, P.; Radtke, A. Silver Nanoparticles Fabricated Using Chemical Vapor Deposition and Atomic Layer Deposition Techniques: Properties, Applications and Perspectives: Review. In *Noble and Precious Metals—Properties, Nanoscale Effects and Applications*; IntechOpen: London, UK, 2018.
27. Wan, Y.; Raman, S.; He, F.; Huang, Y. Surface modification of medical metals by ion implantation of silver and copper. *Vacuum* **2007**, *81*, 1114–1118. [CrossRef]
28. Spange, S.; Pfuch, A.; Wiegand, C.; Beier, O.; Hipler, U.C.; Grünler, B. Atmospheric pressure plasma CVD as a tool to functionalise wound dressings. *J. Mater. Sci. Mater. Electron.* **2015**, *26*. [CrossRef]
29. Charitidis, C.A.; Georgiou, P.; Koklioti, M.A.; Trompeta, A.-F.; Markakis, V. Manufacturing nanomaterials: From research to industry. *Manuf. Rev.* **2014**, *1*, 11. [CrossRef]
30. Rashid, H.; Mansoor, M.A.; Haider, B.; Nasir, R.; Hamid, S.B.A.; Abdulrahman, A. Synthesis and characterization of magnetite nano particles with high selectivity using in-situ precipitation method. *Sep. Sci. Technol.* **2019**, *55*, 1207–1215. [CrossRef]
31. Raab, C.; Simkó, M.; Fiedeler, U.; Nentwich, M.; Gazsó, A. Production of nanoparticles and nanomaterials. *Nano Trust* **2011**, *6*, 4.
32. Ismail, A.; Menazea, A.; Kabary, H.A.; El-Sherbiny, A.; Samy, A. The influence of calcination temperature on structural and antimicrobial characteristics of zinc oxide nanoparticles synthesized by Sol–Gel method. *J. Mol. Struct.* **2019**, *1196*, 332–337. [CrossRef]
33. Khan, M.F.; Ansari, A.H.; Hameedullah, M.; Ahmad, E.; Husain, F.M.; Zia, Q.; Baig, U.; Zaheer, M.R.; Alam, M.M.; Khan, A.M.; et al. Sol-gel synthesis of thorn-like ZnO nanoparticles endorsing mechanical stirring effect and their antimicrobial activities: Potential role as nano-antibiotics. *Sci. Rep.* **2016**, *6*, 27689. [CrossRef] [PubMed]
34. Huang, K.-M.; Lin, Z.; Yang, X. Numerical simulation of microwave heating on chemical reaction in dilute solution. *Prog. Electromagn. Res.* **2004**, *49*, 273–289. [CrossRef]
35. Leonelli, C.; Mason, T.J. Microwave and ultrasonic processing: Now a realistic option for industry. *Chem. Eng. Process. Process. Intensif.* **2010**, *49*, 885–900. [CrossRef]
36. Hasanpoor, M.; Aliofkhazraei, M.; Delavari, H. Microwave-assisted Synthesis of Zinc Oxide Nanoparticles. *Procedia Mater. Sci.* **2015**, *11*, 320–325. [CrossRef]
37. Onwudiwe, D.C. Microwave-assisted synthesis of PbS nanostructures. *Heliyon* **2019**, *5*, e01413. [CrossRef] [PubMed]
38. Hu, B.; Wang, S.-B.; Wang, K.; Zhang, M.; Yu, S.-H. Microwave-Assisted Rapid Facile "Green" Synthesis of Uniform Silver Nanoparticles: Self-Assembly into Multilayered Films and Their Optical Properties. *J. Phys. Chem. C* **2008**, *112*, 11169–11174. [CrossRef]
39. Singh, P.; Kim, Y.-J.; Zhang, D.; Yang, D.-C. Biological Synthesis of Nanoparticles from Plants and Microorganisms. *Trends Biotechnol.* **2016**, *34*, 588–599. [CrossRef]
40. Hernández-Díaz, J.A.; Garza-García, J.J.O.; Zamudio-Ojeda, A.; León-Morales, J.M.; López-Velázquez, J.C.; García-Morales, S. Plant-mediated synthesis of nanoparticles and their antimicrobial activity against phytopathogens. *J. Sci. Food Agric.* **2021**, *101*, 1270–1287. [CrossRef] [PubMed]
41. El-Seedi, H.R.; El-Shabasy, R.M.; Khalifa, S.A.M.; Saeed, A.; Shah, A.; Shah, R.; Iftikhar, F.J.; Abdel-Daim, M.M.; Omri, A.; Hajrahand, N.H.; et al. Metal nanoparticles fabricated by green chemistry using natural extracts: Biosynthesis, mechanisms, and applications. *RSC Adv.* **2019**, *9*, 24539–24559. [CrossRef]
42. Madakka, M.; Jayaraju, N.; Rajesh, N. Mycosynthesis of silver nanoparticles and their characterization. *MethodsX* **2018**, *5*, 20–29. [CrossRef] [PubMed]
43. Yadav, T.P.; Yadav, R.M.; Singh, D.P. Mechanical Milling: A Top Down Approach for the Synthesis of Nanomaterials and Nanocomposites. *Nanosci. Nanotechnol.* **2012**, *2*, 22–48. [CrossRef]
44. Mukhopadhyay, N.; Yadav, T.; Srivastava, O. An investigation on the transformation of the icosahedral phase in the Al-Fe-Cu system during mechanical milling and subsequent annealing. *Philos. Mag. A* **2002**, *82*, 2979–2993. [CrossRef]
45. Kammler, H.K.; Mädler, L.; Pratsinis, S.E. Flame Synthesis of Nanoparticles. *Chem. Eng. Technol.* **2001**, *24*, 583–596. [CrossRef]
46. D'Amato, R.; Falconieri, M.; Gagliardi, S.; Popovici, E.; Serra, E.; Terranova, G.; Borsella, E. Synthesis of ceramic nanoparticles by laser pyrolysis: From research to applications. *J. Anal. Appl. Pyrolysis* **2013**, *104*, 461–469. [CrossRef]

47. Ren, G.; Hu, D.; Cheng, E.W.; Vargas-Reus, M.A.; Reip, P.; Allaker, R.P. Characterisation of copper oxide nanoparticles for antimicrobial applications. *Int. J. Antimicrob. Agents* **2009**, *33*, 587–590. [CrossRef] [PubMed]
48. Zhi, L.; Müllen, K. A bottom-up approach from molecular nanographenes to unconventional carbon materials. *J. Mater. Chem.* **2008**, *18*, 1472–1484. [CrossRef]
49. Park, J.; Ham, S.; Jang, M.; Lee, J.; Kim, S.; Kim, S.; Lee, K.; Park, D.; Kwon, J.; Kim, H.; et al. Spatial-Temporal Dispersion of Aerosolized Nanoparticles During the Use of Consuemr Spray Products and Estimates of Inhalation Exposure. *Environ. Sci. Technol.* **2017**, *51*, 7624–7638. [CrossRef] [PubMed]
50. Smijs, T.G.; Pavel, S. Titanium dioxide and zinc oxide nanoparticles in sunscreens: Focus on their safety and effectiveness. *Nanotechnol. Sci. Appl.* **2011**, *4*, 95–112. [CrossRef] [PubMed]
51. Roduner, E. Size matters: Why nanomaterials are different. *Chem. Soc. Rev.* **2006**, *35*, 583–592. [CrossRef] [PubMed]
52. Issa, B.; Obaidat, I.M.; Albiss, B.A.; Haik, Y. Magnetic Nanoparticles: Surface Effects and Properties Related to Biomedicine Applications. *Int. J. Mol. Sci.* **2013**, *14*, 21266–21305. [CrossRef]
53. Ramalingam, G. *Quantum Confinement*; IntechOpen: London, UK, 2020.
54. Kim, N.H.; Kim, J.-Y.; Ihn, K.J. Preparation of Silver Nanoparticles Having Low Melting Temperature Through a New Synthetic Process without Solvent. *J. Nanosci. Nanotechnol.* **2007**, *7*, 3805–3809. [CrossRef]
55. Loulijat, H.; Zerradi, H.; Mizani, S.; Achhal, E.M.; Dezairi, A.; Ouaskit, S. The behavior of the thermal conductivity near the melting temperature of copper nanoparticle. *J. Mol. Liq.* **2015**, *211*, 695–704. [CrossRef]
56. Rostami-Charati, F.; Akbari, R. ZnO-nanoparticles as an Efficient Catalyst for the Synthesis of Functionalized Benzenes: Multi-component Reactions of Sulfonoketenimides. *Comb. Chem. High Throughput Screen.* **2017**, *20*, 781–786. [CrossRef]
57. Kumar, B.V.; Naik, H.S.B.; Girija, D. ZnO nanoparticle as catalyst for efficient green one-pot synthesis of coumarins through Knoevenagel condensation. *J. Chem. Sci.* **2011**, *123*, 615–621. [CrossRef]
58. Khan, M.S.; Bhaisare, M.L.; Gopal, J.; Wu, H.-F. Highly efficient gold nanorods assisted laser phototherapy for rapid treatment on mice wound infected by pathogenic bacteria. *J. Ind. Eng. Chem.* **2016**, *36*, 49–58. [CrossRef]
59. Millenbaugh, N.J.; Baskin, J.B.; DeSilva, M.N.; Elliott, W.R.; Glickman, R.D. Photothermal killing of Staphylococcus aureus using antibody-targeted gold nanoparticles. *Int. J. Nanomed.* **2015**, *10*, 1953–1960. [CrossRef] [PubMed]
60. Kirui, D.K.; Weber, G.; Talackine, J.; Millenbaugh, N.J. Targeted laser therapy synergistically enhances efficacy of antibiotics against multi-drug resistant Staphylococcus aureus and Pseudomonas aeruginosa biofilms. *Nanomed. Nanotechnol. Biol. Med.* **2019**, *20*, 102018. [CrossRef] [PubMed]
61. Evanoff, D.D.; Chumanov, G. Synthesis and Optical Properties of Silver Nanoparticles and Arrays. *ChemPhysChem* **2005**, *6*, 1221–1231. [CrossRef]
62. Rastinehad, A.R.; Anastos, H.; Wajswol, E.; Winoker, J.S.; Sfakianos, J.P.; Doppalapudi, S.K.; Carrick, M.R.; Knauer, C.J.; Taouli, B.; Lewis, S.C.; et al. Gold nanoshell-localized photothermal ablation of prostate tumors in a clinical pilot device study. *Proc. Natl. Acad. Sci. USA* **2019**, *116*, 18590–18596. [CrossRef]
63. Qiao, Y.; Ma, F.; Liu, C.; Zhou, B.; Wei, Q.; Li, W.; Zhong, D.; Li, Y.; Zhou, M. Near-Infrared Laser-Excited Nanoparticles To Eradicate Multidrug-Resistant Bacteria and Promote Wound Healing. *ACS Appl. Mater. Interfaces* **2018**, *10*, 193–206. [CrossRef]
64. Parak, W.J.; Gerion, D.; Pellegrino, T.; Zanchet, D.; Micheel, C.; Williams, S.C.; Boudreau, R.; Le Gros, M.A.; Larabell, C.A.; Alivisatos, A.P. Biological applications of colloidal nanocrystals. *Nanotechnology* **2003**, *14*, R15–R27. [CrossRef]
65. Lea, M.C. ART. L.—On Allotropic Forms of Silver. *Am. J. Sci.* **1889**, *37*, 476. [CrossRef]
66. Frens, G.; Overbeek, J.T.G. Carey Lea's colloidal silver. *Kolloid Z. Z. Polym.* **1969**, *233*, 922–929. [CrossRef]
67. Dong, X.; Ji, X.; Wu, H.; Zhao, L.; Li, J.; Yang, W. Shape Control of Silver Nanoparticles by Stepwise Citrate Reduction. *J. Phys. Chem. C* **2009**, *113*, 6573–6576. [CrossRef]
68. Clement, J.L.; Jarrett, P.S. Antibacterial Silver. *Met. Based Drugs* **1994**, *1*, 467–482. [CrossRef]
69. Chopra, I. The increasing use of silver-based products as antimicrobial agents: A useful development or a cause for concern? *J. Antimicrob. Chemother.* **2007**, *59*, 587–590. [CrossRef]
70. Sharma, G.; Kumar, A.; Sharma, S.; Naushad, M.; Dwivedi, R.P.; Alothman, Z.A.; Mola, G.T. Novel development of nanoparticles to bimetallic nanoparticles and their composites: A review. *J. King Saud Univ. Sci.* **2019**, *31*, 257–269. [CrossRef]
71. Abd-Elsalam, K.A.; Hashim, A.F.; Alghuthaymi, M.A. Bimetallic nanoparticles as antimicrobials. *J. Nanotechnol. Mater. Sci.* **2016**, *3*, 1–2. [CrossRef]
72. Dizaj, S.M.; Lotfipour, F.; Barzegar-Jalali, M.; Zarrintan, M.H.; Adibkia, K. Antimicrobial activity of the metals and metal oxide nanoparticles. *Mater. Sci. Eng. C* **2014**, *44*, 278–284. [CrossRef] [PubMed]
73. Morones, J.R.; Elechiguerra, J.L.; Camacho, A.; Holt, K.; Kouri, J.B.; Ramírez, J.T.; Yacaman, M.J. The bactericidal effect of silver nanoparticles. *Nanotechnology* **2005**, *16*, 2346–2353. [CrossRef] [PubMed]
74. Park, M.V.; Neigh, A.M.; Vermeulen, J.P.; De La Fonteyne, L.J.; Verharen, H.W.; Briedé, J.J.; Van Loveren, H.; De Jong, W.H. The effect of particle size on the cytotoxicity, inflammation, developmental toxicity and genotoxicity of silver nanoparticles. *Biomaterials* **2011**, *32*, 9810–9817. [CrossRef]
75. Sondi, I.; Salopek-Sondi, B. Silver nanoparticles as antimicrobial agent: A case study on E. coli as a model for Gram-negative bacteria. *J. Colloid Interface Sci.* **2004**, *275*, 177–182. [CrossRef]
76. Jo, Y.-K.; Kim, B.H.; Jung, G. Antifungal Activity of Silver Ions and Nanoparticles on Phytopathogenic Fungi. *Plant Dis.* **2009**, *93*, 1037–1043. [CrossRef]

77. Egger, S.; Lehmann, R.P.; Height, M.J.; Loessner, M.J.; Schuppler, M. Antimicrobial Properties of a Novel Silver-Silica Nanocomposite Material. *Appl. Environ. Microbiol.* **2009**, *75*, 2973–2976. [CrossRef]
78. Kim, J.S.; Kuk, E.; Yu, K.N.; Kim, J.H.; Park, S.J.; Lee, H.J.; Kim, S.H.; Park, Y.K.; Park, Y.H.; Hwang, C.Y.; et al. Antimicrobial effects of silver nanoparticles. *Nanomed. Nanotechnol. Biol. Med.* **2007**, *3*, 95–101. [CrossRef] [PubMed]
79. 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. Microbiol.* **2007**, *73*, 1712–1720. [CrossRef] [PubMed]
80. Bera, R.; Mandal, S.; Raj, C. Antimicrobial activity of fluorescent Ag nanoparticles. *Lett. Appl. Microbiol.* **2014**, *58*, 520–526. [CrossRef] [PubMed]
81. Lara, H.H.; Ayala-Núñez, N.V.; Turrent, L.D.C.I.; Padilla, C.R. Bactericidal effect of silver nanoparticles against multidrug-resistant bacteria. *World J. Microbiol. Biotechnol.* **2009**, *26*, 615–621. [CrossRef]
82. 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*, 1. [CrossRef] [PubMed]
83. Stevenson, J.; Barwinska-Sendra, A.; Tarrant, E.; Waldron, K.J. Mechanism of action and applications of the antimicrobial properties of copper. In *Microbial Pathogens and Strategies for Combating Them: Science, Technology and Education*; Formatex Research Center: Norristown, PA, USA, 2013; pp. 468–479.
84. Palza, H. Antimicrobial Polymers with Metal Nanoparticles. *Int. J. Mol. Sci.* **2015**, *16*, 2099–2116. [CrossRef] [PubMed]
85. Blecher, K.; Nasir, A.; Friedman, A. The growing role of nanotechnology in combating infectious disease. *Virulence* **2011**, *2*, 395–401. [CrossRef]
86. Tkeshelashvili, L.K.; McBride, T.; Spence, K.; Loeb, L.A. Mutation spectrum of copper-induced DNA damage. *J. Biol. Chem.* **1991**, *266*, 6401–6406. [CrossRef]
87. Macomber, L.; Imlay, J.A. The iron-sulfur clusters of dehydratases are primary intracellular targets of copper toxicity. *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 8344–8349. [CrossRef]
88. Yoon, K.-Y.; Byeon, J.H.; Park, J.-H.; Hwang, J. Susceptibility constants of Escherichia coli and Bacillus subtilis to silver and copper nanoparticles. *Sci. Total Environ.* **2007**, *373*, 572–575. [CrossRef]
89. Ruparelia, J.P.; Chatterjee, A.K.; Duttagupta, S.P.; Mukherji, S. Strain specificity in antimicrobial activity of silver and copper nanoparticles. *Acta Biomater.* **2008**, *4*, 707–716. [CrossRef] [PubMed]
90. El Zowalaty, M.; Ibrahim, N.A.; Salama, M.; Shameli, K.; Usman, M.; Zainuddin, N. Synthesis, characterization, and antimicrobial properties of copper nanoparticles. *Int. J. Nanomed.* **2013**, *8*, 4467–4479. [CrossRef] [PubMed]
91. Mahapatra, O.; Bhagat, M.; Gopalakrishnan, C.; Arunachalam, K.D. Ultrafine dispersed CuO nanoparticles and their antibacterial activity. *J. Exp. Nanosci.* **2008**, *3*, 185–193. [CrossRef]
92. Ahamed, M.; Alhadlaq, H.; Khan, M.A.M.; Karuppiah, P.; Al-Dhabi, N.A. Synthesis, Characterization, and Antimicrobial Activity of Copper Oxide Nanoparticles. *J. Nanomater.* **2014**, *2014*, 1–4. [CrossRef]
93. Saraf, R. Cost effective and Monodispersed Zinc Oxide Nanoparticles Synthesis and their Characterization. *Int. J. Adv. Appl. Sci.* **2013**, *2*, 85–88. [CrossRef]
94. Zhang, Y.; Nayak, T.R.; Hong, H.; Cai, W. Biomedical Applications of Zinc Oxide Nanomaterials. *Curr. Mol. Med.* **2013**, *13*, 1633–1645. [CrossRef]
95. Azam, A.; Ahmed, A.S.; Oves, M.; Khan, M.S.; Habib, S.S.; Memic, A. Antimicrobial activity of metal oxide nanoparticles against Gram-positive and Gram-negative bacteria: A comparative study. *Int. J. Nanomed.* **2012**, *7*, 6003–6009. [CrossRef]
96. Zhang, L.; Ding, Y.; Povey, M.; York, D. ZnO nanofluids–A potential antibacterial agent. *Prog. Nat. Sci.* **2008**, *18*, 939–944. [CrossRef]
97. Li, Y.; Niu, J.; Zhang, W.; Zhang, L.; Shang, E. Influence of Aqueous Media on the ROS-Mediated Toxicity of ZnO Nanoparticles toward Green Fluorescent Protein-Expressing Escherichia coli under UV-365 Irradiation. *Langmuir* **2014**, *30*, 2852–2862. [CrossRef] [PubMed]
98. Sawai, J.; Shoji, S.; Igarashi, H.; Hashimoto, A.; Kokugan, T.; Shimizu, M.; Kojima, H. Hydrogen peroxide as an antibacterial factor in zinc oxide powder slurry. *J. Ferment. Bioeng.* **1998**, *86*, 521–522. [CrossRef]
99. Sawai, J.; Kawada, E.; Kanou, F.; Igarashi, H.; Hashimoto, A.; Kokugan, T.; Shimizu, M. Detection of active oxygen generated from ceramic powders having antibacterial activity. *J. Chem. Eng. Jpn.* **1996**, *29*, 627–633. [CrossRef]
100. Jiang, W.; Mashayekhi, H.; Xing, B. Bacterial toxicity comparison between nano- and micro-scaled oxide particles. *Environ. Pollut.* **2009**, *157*, 1619–1625. [CrossRef]
101. Padmavathy, N.; Vijayaraghavan, R. Enhanced bioactivity of ZnO nanoparticles—an antimicrobial study. *Sci. Technol. Adv. Mater.* **2008**, *9*, 035004. [CrossRef]
102. Vargas-Reus, M.A.; Memarzadeh, K.; Huang, J.; Ren, G.G.; Allaker, R.P. Antimicrobial activity of nanoparticulate metal oxides against peri-implantitis pathogens. *Int. J. Antimicrob. Agents* **2012**, *40*, 135–139. [CrossRef] [PubMed]
103. Bahrami, K.; Nazari, P.; Nabavi, M.; Golkar, M.; Almasirad, A.; Shahverdi, A.R. Hydroxyl capped silver-gold alloy nanoparticles: Characterization and their combination effect with different antibiotics against Staphylococcus aureus. *Nanomed. J.* **2014**, *1*, 155–161.
104. Zhao, Y.; Ye, C.; Liu, W.; Chen, R.; Jiang, X. Tuning the Composition of AuPt Bimetallic Nanoparticles for Antibacterial Application. *Angew. Chem. Int. Ed.* **2014**, *53*, 8127–8131. [CrossRef]

105. Li, H.F.; Qiu, K.J.; Zhou, F.Y.; Li, L.; Zheng, Y.F. Design and development of novel antibacterial Ti-Ni-Cu shape memory alloys for biomedical application. *Sci. Rep.* **2016**, *6*, 37475. [CrossRef] [PubMed]
106. Cai, S.; Jia, X.; Han, Q.; Yan, X.; Yang, R.; Wang, C. Porous Pt/Ag nanoparticles with excellent multifunctional enzyme mimic activities and antibacterial effects. *Nano Res.* **2017**, *1*, 2056–2069. [CrossRef]
107. Cani, P.D. Human gut microbiome: Hopes, threats and promises. *Gut* **2018**, *67*, 1716. [CrossRef] [PubMed]
108. Kapoor, G.; Saigal, S.; Elongavan, A. Action and resistance mechanisms of antibiotics: A guide for clinicians. *J. Anaesthesiol. Clin. Pharmacol.* **2017**, *33*, 300–305. [CrossRef]
109. Dzidic, S.; Suskovic, J.; Kos, B. Antibiotic Resistance Mechanisms in Bacteria: Biochemical and Genetic Aspects. *Food Technol. Biotechnol.* **2008**, *46*, 11–21.
110. Lambert, P.A. Bacterial resistance to antibiotics: Modified target sites. *Adv. Drug Deliv. Rev.* **2005**, *57*, 1471–1485. [CrossRef]
111. Hamilton, S.M.; Alexander, J.A.N.; Choo, E.J.; Basuino, L.; Da Costa, T.M.; Severin, A.; Chung, M.; Aedo, S.; Strynadka, N.C.J.; Tomasz, A.; et al. High-Level Resistance of Staphylococcus aureus to β-Lactam Antibiotics Mediated by Penicillin-Binding Protein 4 (PBP4). *Antimicrob. Agents Chemother.* **2017**, *61*, e02727-16. [CrossRef] [PubMed]
112. Hall, R.M. *Gebe Cassettes in Brenner's Encyclopedia of Genetics*; Elsevier: Amsterdam, The Netherlands, 2013; pp. 177–180.
113. Dzidic, S.; Bedeković, V. Horizontal gene transfer-emerging multidrug resistance in hospital bacteria. *Acta Pharmacol. Sin.* **2003**, *24*, 519–526. [PubMed]
114. Sun, D. Pull in and Push Out: Mechanisms of Horizontal Gene Transfer in Bacteria. *Front. Microbiol.* **2018**, *9*, 2154. [CrossRef] [PubMed]
115. Yin, J.-J.; Liu, J.; Ehrenshaft, M.; Roberts, J.E.; Fu, P.P.; Mason, R.P.; Zhao, B. Phototoxicity of nano titanium dioxides in HaCaT keratinocytes—Generation of reactive oxygen species and cell damage. *Toxicol. Appl. Pharmacol.* **2012**, *263*, 81–88. [CrossRef]
116. Shleev, S.; Tkac, J.; Christenson, A.; Ruzgas, T.; Yaropolov, A.I.; Whittaker, J.W.; Gorton, L. Direct electron transfer between copper-containing proteins and electrodes. *Biosens. Bioelectron.* **2005**, *20*, 2517–2554. [CrossRef]
117. Sintubin, L.; De Windt, W.; Dick, J.; Mast, J.; Van Der Ha, D.; Verstraete, W.; Boon, N. Lactic acid bacteria as reducing and capping agent for the fast and efficient production of silver nanoparticles. *Appl. Microbiol. Biotechnol.* **2009**, *84*, 741–749. [CrossRef]
118. Kim, D.H.; Park, J.C.; Jeon, G.E.; Kim, C.S.; Seo, J.H. Efect of the size and shape of silver nanoparticles on bacterial growth and metabolism by monitoring optical density and fluorescence intensity. *Biotechnol. Bioprocess Eng.* **2017**, *22*, 210–217. [CrossRef]
119. Deng, X.; Huang, Z.; Wang, W.; Davé, R.N. Investigation of nanoparticle agglomerates properties using Monte Carlo simulations. *Adv. Powder Technol.* **2016**, *27*, 1971–1979. [CrossRef]
120. Fortescue-Brickdale, J.M. Collargol: A Review of Some of Its Clinical Applications, with Experiments on Its Antiseptic Action. *Bristol Med. Chir. J.* **1903**, *21*, 337–344. [PubMed]
121. Fung, M.C.; Bowen, D.L. Silver Products for Medical Indications: Risk-Benefit Assessment. *J. Toxicol. Clin. Toxicol.* **1996**, *34*, 119–126. [CrossRef] [PubMed]
122. Pulit-Prociak, J.; Banach, M. Silver nanoparticles—A material of the future . . . ? *Open Chem.* **2016**, *14*, 76–91. [CrossRef]
123. Lem, K.W.; Choudhury, A.; Lakhani, A.A.; Kuyate, P.; Haw, J.R.; Lee, D.S.; Iqbal, Z.; Brumlik, C.J. Use of nanosilver in consumer products. *Recent Pat. Nanotechnol.* **2012**, *6*, 60–72. [CrossRef] [PubMed]
124. Callewaert, C.; De Maeseneire, E.; Kerckhof, F.-M.; Verliefde, A.; Van De Wiele, T.; Boon, N. Microbial Odor Profile of Polyester and Cotton Clothes after a Fitness Session. *Appl. Environ. Microbiol.* **2014**, *80*, 6611–6619. [CrossRef] [PubMed]
125. Baker, L.B. Sweating Rate and Sweat Sodium Concentration in Athletes: A Review of Methodology and Intra/Interindividual Variability. *Sports Med.* **2017**, *47*, 111–128. [CrossRef]
126. Troccaz, M.; Starkenmann, C.; Niclass, Y.; van de Waal, M.; Clark, A.J. 3-Methly-3-sulfanylhexan-1-ol as a Major Descriptor for the Human Axilla-Sweat Odour Profile. *Chem. Biodivers.* **2004**, *1*, 1022–1035. [CrossRef]
127. Ozeki, C.; Moro, O. A study of the suppression of body odour in elderly subjects by anti-fungal agents. *Int. J. Cosmet. Sci.* **2016**, *38*, 312–318. [CrossRef]
128. Yeo, S.Y.; Lee, H.J.; Jeong, S.H. Preparation of nanocomposite fibers for permanent antibacterial effect. *J. Mater. Sci.* **2003**, *38*, 2143–2147. [CrossRef]
129. Gerber, L.C.; Mohn, D.; Fortunato, G.; Astasov-Frauenhoffer, M.; Imfeld, T.; Waltimo, T.; Zehnder, M.; Stark, W.J. Incorporation of reactive silver-tricalcium phosphate nanoparticles into polyamide 6 allows preparation of self-disinfecting fibers. *Polym. Eng. Sci.* **2011**, *51*, 71–77. [CrossRef]
130. Zhang, Y.; Li, Y.; Hu, Q. Colourless antibacterial cotton fabrics based on silver nanoparticles and chitosan complexes. *Int. J. Cloth. Sci. Technol.* **2012**, *24*, 118–128. [CrossRef]
131. Bondarenko, O.; Juganson, K.; Ivask, A.; Kasemets, K.; Mortimer, M.; Kahru, A. Toxicity of Ag, CuO and ZnO nanoparticles to selected environmentally relevant test organisms and mammalian cells in vitro: A critical review. *Arch. Toxicol.* **2013**, *87*, 1181–1200. [CrossRef] [PubMed]
132. Muzslay, M.; Ali, S.; Wilson, P. 1382Antimicrobial efficacy of Corning® Gorilla® Glass 3 under laboratory conditions. *Open Forum Infect. Dis.* **2014**, *1*, S363. [CrossRef]
133. Hodges, K.; Gill, R. Infectious diarrhea. *Gut Microbes* **2010**, *1*, 4–21. [CrossRef] [PubMed]
134. Ahmed, J.; Arfat, Y.A.; Bher, A.; Mulla, M.; Jacob, H.; Auras, R. Active Chicken Meat Packaging Based on Polyactide Films and Bimetallic Ag-Cu Nanoparticles and Essential Oil. *J. Food Sci.* **2018**, *83*, 1299–1310. [CrossRef] [PubMed]

135. Emamifar, A.; Kadivar, M.; Shahedi, M.; Soleimanian-Zad, S. Effect of nanocomposite packaging containing Ag and ZnO on inactivation of Lactobacillus plantarum in orange juice. *Food Control.* **2010**, *22*, 408–413. [CrossRef]
136. An, J.; Zhang, M.; Wang, S.; Tang, J. Physical, chemical and microbiological changes in stored green asparagus spears as affected by coating of silver nanoparticles-PVP. *LWT* **2008**, *41*, 1100–1107. [CrossRef]
137. Weber, D.J.; Anderson, D.; Rutala, W.A. The role of the surface environment in healthcare-associated infections. *Curr. Opin. Infect. Dis.* **2013**, *26*, 338–344. [CrossRef] [PubMed]
138. Kramer, A.; Schwebke, I.; Kampf, G. How long do nosocomial pathogens persist on inanimate surfaces? A systematic review. *BMC Infect. Dis.* **2006**, *6*. [CrossRef]
139. Kumar, A.; Vemula, P.K.; Ajayan, P.M.; John, G.C. Silver-nanoparticle-embedded antimicrobial paints based on vegetable oil. *Nat. Mater.* **2008**, *7*, 236–241. [CrossRef]
140. Gunell, M.; Haapanen, J.; Brobbey, K.J.; Saarinen, J.J.; Toivakka, M.; Mäkelä, J.M.; Huovinen, P.; Eerola, E. Antimicrobial characterization of silver nanoparticle-coated surfaces by "touch test" method. *Nanotechnol. Sci. Appl.* **2017**, *10*. [CrossRef] [PubMed]
141. Ramsden, J.; Reid, M.; Whatley, V.; Dancer, S. Disastrous performance of NanoCote/Aqua Based antimicrobial paint in a hospital setting. *J. Biol. Phys. Chem.* **2016**, *16*, 131–136. [CrossRef]
142. Zhang, S.; Liu, X.; Wang, H.; Peng, J.; Wong, K.K. Silver nanoparticle-coated suture effectively reduces inflammation and improves mechanical strength at intestinal anastomosis in mice. *J. Pediatr. Surg.* **2014**, *49*, 606–613. [CrossRef] [PubMed]
143. Della Valle, C.; Visai, L.; Santin, M.; Cigada, A.; Candiani, G.; Pezzoli, D.; Arciola, C.L.; Imbriani, M.; Chiesa, R. A novel antibacterial modification treatment of titanium capable to improve osseointegration. *Int. J. Artif. Organs* **2012**, *35*, 864–875. [CrossRef]
144. Xia, W.; Grandfield, K.; Hoess, A.; Ballo, A.; Cai, Y.; Engqvist, H. Mesoporous titanium dioxide coating for metallic implants. *J. Biomed. Mater. Res. Part B Appl. Biomater.* **2012**, *100*, 82–93. [CrossRef]
145. Samuel, U.; Guggenbichler, J. Prevention of catheter-related infections: The potential of a new nano-silver impregnated catheter. *Int. J. Antimicrob. Agents* **2004**, *23*, 75–78. [CrossRef] [PubMed]
146. Galiano, K.; Pleifer, C.; Engelhardt, K.; Brössner, G.; Lackner, P.; Huck, C.; Lass-Flörl, C.; Obwegeser, A. Silver segregation and bacterial growth of intraventricular catheters impregnated with silver nanoparticles in cerebrospinal fluid drainages. *Neurol. Res.* **2008**, *30*, 285–287. [CrossRef]
147. Yassin, M.A.; Elkhooly, T.A.; Elsherbiny, S.M.; Reicha, F.M.; Shokeir, A.A. Facile coating of urinary catheter with bio–inspired antibacterial coating. *Heliyon* **2019**, *5*, e02986. [CrossRef]
148. Wu, J.; Zheng, Y.; Song, W.; Luan, J.; Wen, X.; Wu, Z.; Chen, X.; Wang, Q.; Guo, S. In situ synthesis of silver-nanoparticles/bacterial cellulose composites for slow-released antimicrobial wound dressing. *Carbohydr. Polym.* **2014**, *102*, 762–771. [CrossRef]
149. Augustine, R.; Kalarikkal, N.; Thomas, S. Electrospun PCL membranes incorporated with biosynthesized silver nanoparticles as antibacterial wound dressings. *Appl. Nanosci.* **2016**, *6*, 337–344. [CrossRef]
150. Paladini, F.; Pollini, M. Antimicrobial Silver Nanoparticles for Wound Healing Application: Progress and Future Trends. *Materials* **2019**, *12*, 2540. [CrossRef] [PubMed]