processes

Review

Copper and Copper Nanoparticles Applications and Their Role against Infections: A Minireview

Iliana A. Ivanova [1], Dragomira S. Daskalova [1], Lilia P. Yordanova [1] and Elitsa L. Pavlova [2,3,*]

1 Faculty of Biology, Sofia University "St. Kliment Ohridski", 8 Dragan Tsankov Blvd., 1164 Sofia, Bulgaria
2 Faculty of Physics, Sofia University "St. Kliment Ohridski", 5 James Boucher Blvd., 1164 Sofia, Bulgaria
3 Center of Competence "Clean Technologies for Sustainable Environment—Water, Waste, Energy for Circular Economy", 1000 Sofia, Bulgaria
* Correspondence: elli_pavlova@abv.bg

Abstract: The focus of this review article is to present a retrospective analysis of copper applications focusing on ions and nanoparticles as broad-spectrum antimicrobials. Copper nanoparticles are presented as an alternative to rising antibiotic resistance. The basic mechanisms of bacterial, fungal, and viral inactivation, which explain their potential, are presented. The green biosynthesis of copper nanoparticles using biomaterials is also presented and considered a very promising trend for future biotechnology and medical applications.

Keywords: antibacterial; antifungal; antiviral; copper; nanoparticles; coatings

check for updates

Citation: Ivanova, I.A.; Daskalova, D.S.; Yordanova, L.P.; Pavlova, E.L. Copper and Copper Nanoparticles Applications and Their Role against Infections: A Minireview. *Processes* **2024**, *12*, 352. https://doi.org/10.3390/pr12020352

Academic Editor: Fabio Carniato

Received: 14 December 2023
Revised: 27 January 2024
Accepted: 5 February 2024
Published: 7 February 2024

1. Introduction and History of Copper Applications in the Prevention and Treatment of Infections

The Smith Papyrus, the oldest known medical document in history, presents the first documented use of copper as an anti-infection agent. The information there is attributed to an Egyptian physician around 1700 BC, but is based on information even since 3200 BC. In hieroglyphics, copper was denoted by the ankh symbol, which was used by the Egyptians and Indians to symbolize endless life. They used various forms of copper and copper compounds to maintain hygiene for many ailments. In ancient times, the Egyptians used to sterilize wounds and drink water by applying metals (silver, copper, etc.) [1].

As early as 1600 BC, the Chinese utilized copper coins as medicine to cure bladder problems and stomach and heart aches. To keep battle wounds from infection, Phoenician sailors sprinkled shavings from their bronze swords inside.

Women have known for thousands of years that storing water in copper vessels protected their children from diarrhea, and kept this knowledge for the next generations. The Romans described various medicinal applications of copper. Copper compounds were also used by the Aztecs to heal sore throats; in Persia and India, copper was applied to treat venereal ulcers, boils, and eye infections [2].

The power of copper's antimicrobial effect is extraordinary. A team of scientists checked the old railings of the Grand Central Terminal in New York and found that the copper still works just as well as the day it was installed more than a hundred years ago, and the antimicrobial effect still remains.

Copper kills the bacteria that cause Legionnaires' disease, as well as drug-resistant microorganisms such as methicillin-resistant *Staphylococcus aureus* (MRSA). Viruses concerning the global health community, such as the Middle East Respiratory Syndrome (MERS), the 2009 swine flu pandemic (H1N1), and the 2019 pandemic (SARS-CoV-2) have been shown to die from contact with pure copper in minutes [3–8]. Ahmadi et al. revealed the antiviral efficacy of copper nanoparticles biosynthesized by Juglans regia green husk aqueous extracts and the synergistic action of copper and iron nanoparticles on viruses [9].

Patoo et al. and Rai et al. [10,11] also contributed with proofs to the synergistic effects of metal and metal oxide nanoparticles on SARS-CoV-2 and other viruses.

2. Methods for the Synthesis of Copper Nanoparticles

There are basically three groups of methods for nanoparticle synthesis: physical, chemical, and biological [12]. One of the physical methods that is most preferred and popular among authors is radio frequency magnetron sputtering. This is one of the most promising methods for applying thin layers due to the possibility of obtaining a homogeneous coating over a large area under controllable conditions [13]. The main disadvantage of this outdated method is related to the high cost of nanoparticle synthesis [14]. This method also allows the co-pulverization of the newly synthesized nanomaterials, which leads to an important characteristic: the antimicrobial activity [15].

According to Hachem et al. [16], the synthesis of nanoparticles using chemical methods is based on fundamental chemical reactions. These reactions are precipitation, oxidation, hydrolysis, thermolysis, polymerization, and condensation [17]. Depending on the reactions, several preferred chemical methods for synthesis stand out. One of them is plasma chemical vapor deposition, which is used to deposit thin films from a gaseous to a solid state over a substrate [18]. Another widely used technique is the "sol-gel" method. This technique is applied to obtain metal oxides, mostly copper nanoparticles [19,20]. Chemical deposition is one of the most economical techniques for acquiring nanoparticles because it does not depend on expensive machinery and equipment [21]. "Green" chemical synthesis is an innovative and relatively new method for the synthesis of metallic nanomaterials, where water, which contains environmentally friendly reducing agents, is used as a chemical solvent [22].

3. Green Synthesis of Copper Nanoparticles

"Green synthesis" controls the size and shape as well as the production of stable nanomaterials without harmful reagents. Biological synthesis is superior to chemical and physical methods in terms of cost, environmental friendliness, and ease of synthesis screening. "Green synthesis" is ecological, economical, and safe and uses biological materials such as cell cultures of bacteria, fungi, and plants [23]. Several factors affect this method, including the temperature, pH, reaction time, volume of reagents added, and volume of the biological extract. The interaction of these factors is critical for determining the shape and size of the synthesized nanoparticles. Various plants and their parts are excellent producers of copper nanoparticles, such as the leaf extract of *Hagenia abyssinica* L., the juice of *Citrus medica* Linn., and *Syzygium guineense* [24–26]. The plants are excellent producers of copper nanoparticles because they are widely available, easy to process, and a source of many metabolites. They are rich in pharmacological constituents that act as both reducing and capping agents in the process of synthesis [24–26].

Over the past few decades, chemical and physical synthesis approaches have been widely used to produce nanoparticles [27]. However, they have been proven to be dangerous to both the environment and human health because of the harsh chemicals used. Biosynthesis technologies have been identified as potential and optimal alternatives. These approaches hold promise in a variety of contexts, including green chemistry. For example, copper nanoparticles can be produced in large quantities using Rhatany root extract as a "renewable resource" [26]. The literature review reveals that biologically synthesized copper nanoparticles using microbial substances instead of plant extracts are sparsely explored. Future research can be focused in this direction because "green synthesis" appears to be the future of nanotechnology synthesis.

4. Copper Ions and Nanoparticles

The majority of research on metal-based nano-antimicrobials has demonstrated that the nanomaterial's biological efficacy is much greater and longer than the metal salt's bioactivity. Numerous factors can affect this effect, including the size of the nanoparticles, the high surface-to-volume ratio of ultrafine particles, the massive release of ions, as well as the unusual features connected to the existence of surface stabilizers. Anti-agglomeration compounds, in fact, have frequently been shown to modify the ion release of the nanoparticles and, consequently, their antibacterial characteristics [23,27–30].

It has been demonstrated that soluble copper compounds exhibit superior antibacterial activity against a variety of pathogens, such as viruses, bacteria, fungi, and algae [5,7–9], all of which are generally safe for medical implants and human consumption [31–33]. Copper primarily enters microbial cells in the form of ions [28–30]. It alters the pH level and function of the membrane channels, destroys the functional groups and structure of the cell and inner membranes, and produces reactive oxygen species (ROS) that can cause irreversible damages like protein oxidation, the rupture of crucial internal molecules like enzymes, DNA, and RNA, and the destruction of the entire cell membrane due to free-radical lipid peroxidation (Figure 1).

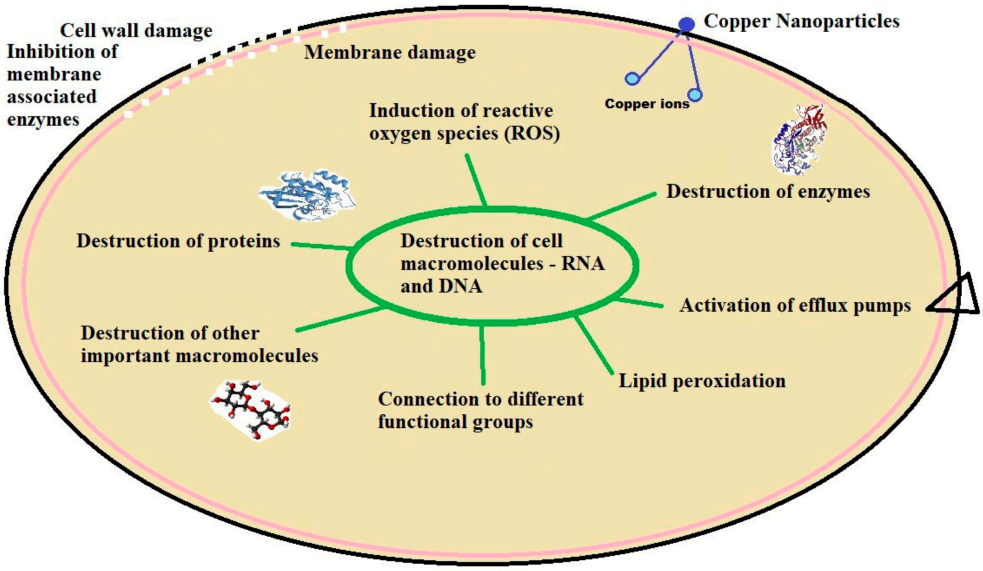

Figure 1. Effect of copper nanoparticles and ions on a microbial cell.

Longano et al. [34] have outlined several methods for producing copper nanoparticles with varying sizes, shapes, and coatings attached to various polymers. Torras and Roig [35] present contemporary techniques for using microwaves to manufacture copper and alloyed copper particles and trace their photocatalytic activity. One of the most prevalent uses of this metal in contemporary healthcare facilities is the control of Legionella sp. in hospital water distribution systems by the ionization method of copper and silver [36–40]. A broad spectrum of bacteria, including spore-forming *Bacillus subtilis*, *Salmonella enterica*, *Campilobacter jejuni*, *Escherichia coli*, and *Staphylococcus aureus*, are susceptible to the antimicrobial activity of copper ions originating from nanoparticles. Moreover, 99.9% of most bacteria are killed within two hours of contact [37–39,41,42]. Additionally, this metal occasionally exhibits superior qualities in comparison to other precious metals with antibacterial activity, like platinum and gold [40,43]. By direct contact, bacteria, yeasts, and viruses can be eliminated from copper surfaces. According to reports, contact death happens over a prolonged incubation period and at a pace of at least seven to eight orders of magnitude per hour. There were no live microbes found on copper surfaces. This gives rise to the concept of self-cleaning materials made of copper [36]. Additionally, copper is a vital trace element for human health since it is regarded as a metal that is not too harmful to humans and is utilized in intrauterine and other devices [37,38]. Some authors claim that copper nanoparticles cause severe toxicological effects and serious damage to the kidneys, liver, and spleen of experimental mice, but micro-copper particles do not do so in the majority [40]. There is a relationship between the characteristics of nanomaterials and their nanotoxicity [43]. Several factors, such as the specific surface area of the nanoparticles, their high reactivity, the overexpression of H^+, etc., are predicted to probably cause the severe nanotoxicity observed in vivo [43]. It should be experimented further in vivo by green synthesized copper nanoparticles to check their toxicity completely.

Synthesized copper nanoparticles against *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Bacillus subtilis* have exceptional antibacterial capabilities, thanks to an extract from the leaves of the herb *Hagenia abyssinica* [44]. According to Ganga's research, gram-positive bacteria like *Staphylococcus aureus* and *Bacillus subtilis*, as well as gram-negative bacteria like *Escherichia coli* and *Klebsiella pneumoniae*, were effectively neutralized by green-synthesized copper nanoparticles derived from *Riccia fluitans* bryophytes [45]. From all the combinations tested against the targeted bacterial strains, copper nanoparticles demonstrated the strongest antibacterial efficacy. Similar outcomes were observed by Malaikozhundan et al. [46] when copper nanoparticles were synthesized using *Mentha spicata* leaf extract to inhibit *Klebsiella pneumoniae, Escherichia coli*, and the gram-positive *Streptococcus pyogenes* and *Staphylococcus aureus*.

5. Gene Expression after Nanoparticle Interaction

Reverse transcriptase polymerase chain reaction about gene expression induced the activation of copper oxidase, converting the toxic first-valence copper ions into less toxic second-valence ions. The activation was observed in the fifth minute of the interaction of bacterial cells with copper and silver ions. A statistically significant activation of copper oxidase was found in *E. coli* ATCC 10536 and in the presence of titanium dioxide thin films embedded with copper and silver nanoparticles by RT-qPCR, despite the significantly lower concentration of ions released from the thin film.

The representativeness of these results is ensured by the use of two types of negative controls: the so-called clear glass plate (uncoated but cleaned as for coating) and the titanium dioxide-coated one. The gene expression was similar when tested against the control, pure glass, or TiO_2. This allows us to conclude that TiO_2 does not act as a stress-determining factor and that the occurrence of stress responses is entirely due to the copper and silver nanoparticles entering the component composition of the thin films' coatings. This confirms that titanium nanoparticles or dissolved ions do not have a suppressive effect on the bacterium. It proves that the dissolution of metal ions from the atomic clusters of copper and silver nanoparticles is responsible for their combined toxic effect [47].

When analyzing the data for 30 and 60 min, the results are comparable. The effect is weaker with time, i.e., the expression of copper oxidase CuO in the first minutes of the treatment is most noticeable. The tendency for a decrease in the expression of copper oxidase with time is clear. The result in the 5th minute shows the rapid reaction of the bacteria to the nanomaterials and the stress response. Nine-fold activation is achieved at the 5th minute, and seven-fold activation is achieved at the 30th minute [47].

6. Combinations between Copper, Copper Oxide, and Other Nanoparticles

Copper nanoparticles could be applied to critical points in some key industries to improve the quality of protective clothing [48]. Several reported studies have given promising results. The Cu-SiO_2 nanocomposite, copper-doped hydroxyapatite nanopowders, alginate nano-copper cotton cellulose fibers, and copper nanoparticle-treated fibers were all tested for antibacterial activity using the agar diffusion test [34]. The antibacterial performance results of the fibers loaded with nano-copper demonstrated a distinct zone of inhibition surrounding the visible copper nanoparticle fiber bundle and a reduced number of microbiological colonies. Grace et al. also reported another clear concentration effect [49]. The same scientists demonstrated in a different work that cotton-cellulose fibers treated with nano-copper alginates efficiently prevented the growth of bacteria [31]. CuO nanocomposites completely inhibited the development of *E. coli* cells when applied to cotton fibers [50]. The addition of CuO nanoparticles at doses of 0.01–0.5% and 1% to adhesive composite trans bond XT increased its antibacterial properties against *Streptococcus* mutans. The shear bond strength of the metal brackets linked to the human premolars did not exhibit any negative consequences [51].

Copper alloys can be created by combining copper nanoparticle coatings with other metals. The US Environmental Protection Agency has registered over 450 alloys that are resistant to six different kinds of bacteria, including MRSA, VRE (*Vancomycin-resistant Enterococcus faecium*), *P. aeruginosa*, *S. aureus*, and *E. coli*. Copper-containing coatings can be applied to any surface that is in contact with pathogens and come in a variety of colors and shapes. They do not need expensive extra cleaning techniques and are robust, recyclable, and sustainable. These surfaces work incredibly well; MRSA at 10^6 CFU/mL was eliminated in 90 min at 25 °C on a C197 copper surface when it was contaminated by sneezing and splashing. For clean copper surfaces with 10^6 CFU at 22 °C, a 45-min elimination period in a dry touch simulation yields a faster effect. At 4 °C, complete disinfection is accomplished in 6 h [52].

At 20 °C and 50% relative humidity, copper surfaces were more effective in eradicating MRSA than silver and iron-containing materials and stainless-steel surfaces, with almost no live bacteria remaining 75 min after the microbial application to the studied surface [53]. Within 10 min, an even quicker bactericidal response was seen for vancomycin-resistant *Enterococcus* (VRE) [54]. The increased effectiveness of contact bacterial inactivation on copper surfaces evaluated at higher temperatures and humidity levels is demonstrated by this and other research. Copper nanomaterials generally exhibit quick and wide-ranging biocidal action against a variety of microorganisms, including viruses (*Influenza A* and *Norovirus*), fungi (*Candida albicans*, *Penicillium* sp.), bacteria (*Legionella pneumophila*, *E. coli*, and *Clostridium difficile*—both vegetative cells and spores), as well as resistant strains of these organisms (MRSA, VRE) [2,55]. Due to their multiple non-specific modes of action and quick bactericidal effect, copper-containing contact surfaces are preferred in the fight against resistance in comparison to chemical antibacterial treatments [56,57].

The agar diffusion of the Cu-SiO_2 nanocomposite was determined by placing a paper disk saturated with different nanocomposite aqueous suspensions on an agar surface inoculated with *E. coli* (ATCC 25922). Our result showed that the filter paper prevented the nanoparticles' diffusion into the nutrient medium, but the nanocomposite had a stronger antibacterial effect than the copper nanoparticles [57]. The antibacterial activity of Cu-SiO_2 nanocomposites depends on the good distribution and lack of aggregation of the copper nanoparticles on the surface of the SiO_2 nanoparticles [58]. The effectiveness of nanocomposites is also confirmed by the work of Maniprasad and Santra [59], who investigated the antibacterial activity of copper nanoparticles deposited on SiO_2 particles. They estimated a minimum inhibitory concentration (MIC) of 2.4 μg of Cu metal/mL against both *E. coli* and *B. subtilis*. Antibacterial studies clearly present that Cu/SiO_2 nanocomposites are more effective compared to insoluble $Cu(OH)_2$ at equivalent concentrations of copper, indicating the higher bioavailability of ions (i.e., more soluble Cu) in Cu/SiO_2 nanocomposites, determined by the "core-shell" structure. The antimicrobial test of copper-doped hydroxyapatite nanopowders against *E. coli* ATCC 25922 by the agar diffusion method and in liquid media showed that all metal-doped hydroxyapatite samples caused the death of viable bacterial cells [60]. Another study by Yaseen et al. [61] reported that the CuO-SiO_2-nanocomposite had good photocatalytic activity, anti-leishmanial activity, and antioxidant activity, i.e., had promising biological attributes.

Compared to silver, copper coatings have been the subject of less investigated antibacterial activity; however, a Cu/TiO_2 thin film was investigated under low UV light using *E. coli* that is resistant to copper ions. Sunada [62] showed that the synergistic action of the photocatalytic activity of TiO_2 and that of copper ions produced a bactericidal impact of the Cu/TiO_2 combination even on copper-resistant *E. coli* cells under very low UV irradiation. Cu-doped TiO_2 showed superior antibacterial activity against *E. coli* when compared to undoped TiO_2, as reported by Mingmongkol et al. [63]. However, the high Cu doping concentrations of 1.0 wt.% and Cu-doped TiO_2 exhibited detrimental effects on the charge transfer, ·OH generation, and surface charge of the nanoparticles.

Several authors reported about various formulations and combinations of silver and copper nanoparticles and their synergistic effects on different bacteria [64,65]. Other authors reported on the immunomodulatory effects of copper on some proteins, influencing innate host defenses. Zinc, copper, and silver appear to be the metals with the greatest activity in regard to the increased concentration of nitric oxide (NO·), a kind of reactive nitrogen species that has synergistic effects on host immune systems against pathogens [66–68]. Nitric oxide can oxidize copper too. It is present in protective proteins. It may cause the release of copper ions that boost the toxicity against microbial and tumor cells [66,69].

7. Combination of Copper with Polymers for Antimicrobial Effect

Using electro-synthesized copper nanoparticles dissolved in various polymers, as well as ion-deposited composites (Ion Beam Sputtering technique) and copper fluoropolymer nanocomposite films, Cioffi et al. [27] conducted biological studies on *E. coli*. Copper nanoparticles stabilized with tetra-butyl-ammonium perchlorate were found to have clear biostatic activity on *Saccharomyces cerevisiae*, *Escherichia coli*, *Staphylococcus aureus*, and *Lysteria* sp. when they were embedded in polymer matrices like polyvinyl-methyl-ketone, PVC (polyvinyl chloride), and polyvinylidene fluoride. Furthermore, it was consistently noted that copper nanoparticle-polyvinylidene fluoride films had the least effective biostatic action, while copper nanoparticle-polyvinyl-methyl-ketone films exhibited the best biostatic effect [27]. On the other hand, the ammonium salt had a substantial growth inhibition impact and significantly reduced the growth of bacteria in the cases of copper nanoparticles stabilized by tetra-octyl-ammonium chloride and embedded in polymer matrices like polyvinyl-methyl-ketone. It is interesting to note that the simultaneous action of implanted metal nanoparticles and tetra-octyl-ammonium chloride resulted in increased biological activity for these nanocomposites. Furthermore, because of the exceptionally high concentration of unattached copper atoms, copper nanopaticle-polyvinylidene fluoride coatings demonstrated even greater disinfection efficacy against *E. coli* [27].

The antibacterial properties of copper-encrusted multi-walled carbon nanotubes (Cu-MWCNT) were also evaluated in compliance with ISO 14729:2001 (EU) regulations [70]. At a dose of 21 μg/mL, pure MWCNTs showed a comparatively poor impact against *E. coli* (20 ± 2.5%). When compared to pure copper nanoparticles, combined Cu-MWCNTs demonstrated a good level of antibacterial efficiency (~75%) and around 52% bactericidal activity [71]. Copper nanoparticles were functionalized with polyethyleneimine (PEI) and 4-aminobutyric acid (GABA) by Jardón-Maximino et al. [32]. These composites with 2, 5, and 5.0 wt.% of Cu showed outstanding antibacterial action against *Staphylococcus aureus* and *Pseudomonas aeruginosa*. By employing bile juice to create a hemocompatible composite Cu-MWCNT, Mondal and Mondal [33] demonstrated potent antibacterial activity against *S. aureus* and *P. aeruginosa* biofilms, with minimum inhibitory concentrations (MIC) of 24 and 16 μg/mL.

At a lower dosage of approximately 3 μg of Cu per gram composite gel, agarose-Cu nanoparticle composites at two distinct concentrations (3 and 6 μg of Cu per milliliter of LB broth) demonstrated full suppression against *E. coli* [72].

8. Copper Oxide's Biological Effects

According to Perelshtein et al. [50], copper oxide has a very high activity (1.4 wt.%), completely inactivating *S. aureus* and *E. coli* in just 3 h. The toxicity of zinc oxide and titanium oxide was compared with that of nano-sized and powdered copper oxide on the bacteria *Vibrio fischeri*, the water flea *Daphnia magna*, and the freshwater crustacean *Thamnocephalus platyurus*. Compared to the other nanoparticles, the copper nanoparticles were more harmful [73]. The antibacterial properties of cuprous oxide nanoparticles produced with linear low-density polyethylene by co-extrusion, thermal adhesion, and attachment to epoxy resin, three-methoxy-vinyl-silane, and ethyl cyanoacrylate were examined by Gurianov et al. [74]. The impacts of the nanocomposites were ranked as follows: thermal adhesion > ethyl cyanoacrylate > trimethoxyvinylsilane > epoxy resin > extrusion > epoxy resin > produced by extrusion. The composites that exhibit the highest activity may find application as materials for the disinfection of waste-water and tap water.

An enhanced antimicrobial effect was obtained with a combination of TiO_2 with CuO and two-layer structures of Ag and CuO in combination with TiO_2. [57,75–77]. Structures where Ag and CuO are inlaid on TiO_2 have higher biocidal activity.

Fan et al. [68] reported the synergistic antimicrobial effect of copper and silver nanoparticles when mixed and alloyed. The antimicrobial behavior is even better enhanced in Ag–Cu nanoparticles.

9. Mechanisms of Antimicrobial Activity

The antimicrobial properties are attributed to the release of ions from the surface of the metal copper, copper oxide, and nanoparticles, the rate of which mainly depends not only on the chemical composition of the material, but also on the reactive oxygen and nitrogen species (ROS and NS) that are formed. Several mechanisms of action could be outlined [28,42,78].

Copper ions hinder the development of bacterial resistance through many mechanisms simultaneously. The bacterial membranes become damaged when they come into contact with copper surfaces. Copper ions have the ability to directly harm bacterial proteins and, via a Fenton-like reaction, generate extremely reactive hydroxyl radicals (·OH) that interact with other proteins, DNA, and enzymes to cause lipid peroxidation and the destruction of membrane structures [42,79–81]. CuO nanoparticles have been shown to promote advantageous outcomes, including enhanced angiogenesis and wound healing. Through surface functionalization, the surface charge of the nanoparticle can be altered, which contributes to the inactivation of bacteria. Positively charged nanoparticles may bind faster and easily kill bacteria because the bacterial cell wall is, in general, negatively charged [17,28].

An even stronger antimicrobial effect was observed when combining chitosan with copper nanoparticles, and their size depends on the concentration of chitosan [82]. Vanti et al. [83] established 98% fungal growth inhibition at a 0.1% concentration of economically feasible chitosan-coupled copper nanoparticles. The study emphasizes the benefits of synthesized chitosan-copper nanoparticles on agricultural crops as fungicides and growth promoters. It can be a safe alternative to pesticides in order to avoid hazardous effects on the environment [55].

Copper nanoparticles have the potential to be used as antibacterial agents; however, when administered as an aerosol, they cause severe inflammatory reactions and cellular damage. This toxicity may be decreased by coating metal nanoparticles with polysaccharides, such as the antibacterial and biocompatible chitosan. In vitro experiments have demonstrated a considerable reduction in the ROS production and the toxicity of copper nanoparticles after 24 and 52 h when coated with chitosan. In contrast, mice exposed to chitosan-coated as opposed to uncoated copper nanoparticles showed an increase in the inflammatory response presented by the total protein, cytokines/chemokines, and white blood cell count in their broncho-alveolar fluid. These findings imply that covering metal nanoparticles with muco-adhesive polysaccharides (chitosan, for example) may expand their potential for use in the regulated release of copper ions; nevertheless, if inhaled, this will lead to a greater inflammatory response [84,85]. Other studies on the copper-chitosan nanocomposite showed that it had no cytotoxicity on the normal cell line, but exhibited very low cell viability against bladder cancer (UM-UC-3 (transitional cell carcinoma)), squamous cell carcinoma, and transitional cell carcinoma Grade IV cell lines [86].

Copper nanoparticles are mainly used in antiseptic technical materials such as varnishes, paints, and other coatings; for ointments with antimicrobial action in medicine; and also for antiseptic materials in wound healing [28]. In agriculture, the nano-crystalline powders of iron, cobalt, and copper in extremely low concentrations increase the germination rate of seeds as well as the chlorophyll index, the number of nodules, and the yield of the crop [87].

In vitro studies in mice proved that a dose of 430 mg/kg live weight of 23.5 nm copper nanoparticles is lethal. The targets of the attack were the liver, spleen, and kidneys [88]. Exposure to concentrations of 10, 25, and 50 μg/mL of CuO nanoparticles in human pulmonary epithelial cells (A549) resulted in the depletion of glutathione and the stimulation of catalase, lipid peroxidation, and superoxide dismutase activities. The CuO nanoparticles reduced cell viability to 75, 66, and 48%, respectively, according to the MIT assay [89].

The inclusion of copper atoms in the layers of TiO_2 nanoparticles shifts the light absorption to visible light, and therefore irradiation with ultraviolet light is not necessary. The antimicrobial effect is preserved with irradiation with visible light, achieving high bacterial inactivation in 30 min-99.9999% [90]. Qin et al. [91] conducted experiments comparing the antibacterial action of three oxides. The results show that copper oxide is most effective, followed by zinc and finally titanium. Copper oxide nanoparticles work in low concentrations, and it is believed that their action is due to the released copper ions, the generation of ROS, membrane cell disruption, protein and mitochondrial damage, and DNA dysfunction [42].

According to Sandle [92], the control of surfaces as vectors for pathogen transmission increasingly forms part of the overall infection control strategy. In a real hospital setting, various studies have shown that in rooms equipped with copper surfaces, after proper pre-positioning, a reduction in the bacterial load and infection rate is observed [93]. In some studies, it was found that the contact inactivation of bacteria was observed at a rate of 7–8 log/h, with no surviving microorganisms after only a few hours of contact [94]. In 2010, a similar study was conducted at a hospital in Birmingham, UK, where some of the surfaces were replaced with copper alloys. These have been used for an experimental composite toilet seat as well as other key risk items such as door locks, etc.

All the data collected prove that bacteria on copper surfaces are 90–100% less compared to similar plastic and aluminum surfaces. Based on this evidence, many hospital facilities are beginning to use copper or copper alloys for touch surfaces such as door handles, switches and control buttons, tables, bed boards, and hospital cabinets. Furthermore, the use of copper nanoparticles is not limited to hard surfaces; some manufacturers are targeting CuO nanoparticle-impregnated textiles for beds, pillowcases, and hospital clothing for patients and healthcare workers. A clinical trial in intensive care units at Calama Hospital in Chile reported a similar reduction. An ambulatory study confirmed the reduction in the microbial load, resulting in reduced contamination in close proximity to the copper surfaces. The estimate shows a 40% reduction in ICU-acquired infections, with the potential for a reduction of up to 70%. This also leads to reduced care costs and improved patient outcomes [95,96]. After 6 h of exposure, Cu-containing ZnO films led to a strong reduction in the number of viable *E. coli* bacteria in a hospital environment [96–98].

Airborne pathogens are also risky, as are surfaces. Copper nanoparticles are used in heating, ventilation, and air conditioning systems in hospitals. Typically, these systems use aluminum components. Depending on the design and outdoor air pollution, these components can promote the development of resistant biofilms of bacteria and fungi on heat exchanger coils, fins, condensate drains, air ducts, etc. [55,99,100].

10. Conclusions

There is a strong connection between the past applications of copper as a metal and the continuing interest in this material in the following new forms: nanoparticles, alloys with other metals, and combinations with other materials such as polymers, carbon nanotubes, etc. Nanocomposites accumulate promising results, especially in combined activity and synergistic effects with silver, zinc, silica, and titanium dioxide, including ferrite nanoparticles. The nanocomposites with chitosan and other polymers have the advantage of causing less toxicity to mammals but present strong antibacterial, antiviral, and antifungal effects. Copper is improving the immune system's defense against pathogens. Copper will become one of the most precious metals for human well-being. Green synthesized nanoparticles and nanocomposites could be nontoxic for humans as antimicrobials, bioremediation agents, and growth factors for agricultural plants.

11. Future Directions

The future application of green synthesized copper nanoparticles could improve the antimicrobial effect of combined copper nanocomposites and diminish their toxic effect on mammalian cells [34,101,102]. The copper nanoparticles obtained by green synthesis using tea leaf extracts could be used not only for biomedical applications, but also for water bioremediation [103]. Authors obtain copper oxide nanoparticles by "green synthesis" using, for instance, the leaf tissue from *Camellia sinensis* L. and lavender (*Lavandula anguistifolia*). It is proven that they have a successful effect at the lowest concentrations (4 μg mL^{-1}) in the root and shoot development of lettuce and tomato seedlings [104,105]. So, these nanomaterials could be used in the future for bioreclamation and as new fertilizers. The literature review reveals that biologically synthesized copper nanoparticles using plant extract are sparsely explored, and much future research can be conducted in this direction as "green synthesis" is the future of nanotechnology.

Author Contributions: I.A.I., D.S.D. and L.P.Y. have gathered the information and written the text; E.L.P. has reviewed and edited the whole text and supported its publication financially. All authors have read and agreed to the published version of the manuscript.

Funding: The authors acknowledge the financial support of the following projects: "Clean technologies for sustainable environment-waters, waste, energy for circular economy", Ministry of Education and Science, Bulgaria, Contract Number: BG05M2OP001-1.002-0019, "Study of the qualities of borehole waters in Sofia and small settlements around the capital", Scientific Research Fund, Sofia University "St. Kliment Ohridski", Bulgaria, Contract Number: 80-10-174/16.05.2023.

Data Availability Statement: The data presented in this study are available on request from the corresponding author.

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

References

1. Wade, K. The sword and the knife: A comparison of ancient Egyptian treatment of sword injuries and present day knife trauma. *Res Med. J. R. Med. Soc.* **1957**, *24*, 47–56. [CrossRef]
2. Grass, G.; Rensing, C.; Solioz, M. Metallic copper as an antimicrobial surface. *Appl. Environ. Microbiol.* **2011**, *77*, 1541–1547. [CrossRef]
3. Vincent, M.; Duval, R.E.; Hartemann, P.; Engels-Deutsch, M. Contact killing and antimicrobial properties of copper. *J. Appl. Microbiol.* **2018**, *124*, 1032–1046. [CrossRef]
4. Hutasoit, N.; Kennedy, B.; Hamilton, S.; Luttick, A.; Rashid, R.A.R.; Palanisamy, S. Sars-CoV-2 (COVID-19) inactivation capability of copper-coated touch surface fabricated by cold-spray technology. *Manuf. Lett.* **2020**, *25*, 93–97. [CrossRef]
5. Merkl, P.; Long, S.; McInerney, G.M.; Sotiriou, G.A. Antiviral activity of silver, copper oxide and zinc oxide nanoparticle coatings against SARS-CoV-2. *Nanomaterials* **2021**, *11*, 1312. [CrossRef]
6. Jagaran, K.; Singh, M. Nanomedicine for COVID-19: Potential of copper nanoparticles. *Biointerface Res. Appl. Chem.* **2021**, *11*, 10716–10728. [CrossRef]
7. Poggio, C.; Colombo, M.; Arciola, C.R.; Greggi, T.; Scribante, A.; Dagna, A. Copper-alloy surfaces and cleaning regimens against the spread of SARS-CoV-2 in dentistry and orthopedics. From fomites to anti-infective nanocoatings. *Materials* **2020**, *13*, 3244. [CrossRef]
8. Ramos-Zúñiga, J.; Bruna, N.; Pérez-Donoso, J.M. Toxicity mechanisms of copper nanoparticles and copper surfaces on bacterial cells and viruses. *Int. J. Mol. Sci.* **2023**, *24*, 10503. [CrossRef] [PubMed]
9. Ahmadi, M.; Elikaei, A.; Ghadam, P. Antiviral activity of biosynthesized copper nanoparticle by Juglans regia green husk aqueous extract and iron nanoparticle: Molecular docking and in-vitro studies. *Iran J. Microbiol.* **2023**, *15*, 138–148. [CrossRef] [PubMed]
10. Patoo, T.S.; Khanday, F.; Qurashi, A. Prospectus of advanced nanomaterials for antiviral properties. *Mater. Adv.* **2022**, *3*, 2960–2970. [CrossRef]
11. Rai, M.; Deshmukh, S.D.; Ingle, A.P.; Gupta, I.R.; Galdiero, M.; Galdiero, S. Metal nanoparticles: The protective nanoshield against virus infection. *Crit. Rev. Microbiol.* **2016**, *42*, 46–56. [CrossRef]
12. Nam, N.H.; Luong, N.H. Nanoparticles: Synthesis and applications. *Mater. Biomed. Eng.* **2019**, 211–240. [CrossRef]
13. Al-Ghamdi, A.A.; Khedr, M.H.; Ansari, M.S.; Hasan, P.M.Z.; Abdel-Wahab, M.S.; Farghali, A.A. RF Sputtered CuO thin films: Structural, optical and photo-catalytic behavior. *Phys. E Low-Dimens. Syst. Nanostructures* **2016**, *81*, 83–90. [CrossRef]

14. Kim, D.Y.; Kwon, J.H.; Jang, G.S.; Hwang, N.M. Effect of pressure on the film deposition during RF magnetron sputtering considering charged nanoparticles. *Coatings* **2021**, *11*, 132. [CrossRef]
15. Pakpum, C. Preparation of copper thin film mask by sputtering technique assisted by polymer mask photolithography. *IOP Conf. Ser. Mater. Sci. Eng.* **2017**, *213*, 012023. [CrossRef]
16. Hachem, K.; Ansari, M.J.; Saleh, R.O.; Kzar, H.H.; Al-Gazally, M.E.; Altimari, U.S.; Hussein, S.A.; Mohammed, H.T.; Hammid, A.T.; Kianfar, E. Methods of chemical synthesis in the synthesis of nanomaterial and nanoparticles by the chemical deposition method: A review. *BioNanoScience* **2022**, *12*, 1032–1057. [CrossRef]
17. Gawande, M.B.; Goswami, A.; Felpin, F.X.; Asefa, T.; Huang, X.; Silva, R.; Zou, X.; Zboril, R.; Varma, R.S. Cu and Cu-based nanoparticles: Synthesis and applications in catalysis. *Chem. Rev.* **2016**, *116*, 3722–3811. [CrossRef] [PubMed]
18. Dörner, L.; Cancellieri, C.; Rheingans, B.; Walter, M.; Kägi, R.; Schmutz, P.; Kovalenko, M.V.; Jeurgens, L.P. Cost-effective sol-gel synthesis of porous CuO nanoparticle aggregates with tunable specific surface area. *Sci. Rep.* **2019**, *9*, 11758. [CrossRef]
19. Etefagh, R.; Azhir, E.; Shahtahmasebi, N. Synthesis of CuO nanoparticles and fabrication of nanostructural layer biosensors for detecting Aspergillus niger fungi. *Sci. Iran.* **2013**, *20*, 1055–1058. [CrossRef]
20. Patel, M.; Mishra, S.; Verma, R.; Shikha, D. Synthesis of ZnO and CuO nanoparticles via sol gel method and its characterization by using various technique. *Discov. Mater.* **2022**, *2*, 1. [CrossRef]
21. Carlsson, J.-O.; Martin, P.M. Chemical vapor deposition. In *Handbook of Deposition Technologies for Films and Coatings*, 3rd ed.; Martin, P.M., Ed.; Elsevier: Amsterdam, The Netherlands, 2010; Chapter 7; pp. 314–363. ISBN 9780815520313. [CrossRef]
22. Bhattacharya, D.; Gupta, R.K. Nanotechnology and potential of microorganisms. *Crit. Rev. Biotechnol.* **2005**, *25*, 199–204. [CrossRef]
23. Singh, A.; Gautam, P.K.; Verma, A.; Singh, V.; Shivapriya, P.M.; Shivalkar, S.; Sahoo, A.K.; Samanta, S.K. Green synthesis of metallic nanoparticles as effective alternatives to treat antibiotics resistant bacterial infections: A review. *Biotechnol. Rep.* **2020**, *25*, e00427. [CrossRef]
24. Ben Mosbah, M.; Alsukaibi, A.K.D.; Mechi, L.; Alimi, F.; Moussaoui, Y. Ecological synthesis of CuO nanoparticles using *Punica granatum* L. peel extract for the retention of methyl green. *Water* **2022**, *14*, 1509. [CrossRef]
25. Shende, S.; Ingle, A.P.; Gade, A.; Rai, M. Green synthesis of copper nanoparticles by *Citrus medica* Linn. (Idilimbu) juice and its antimicrobial activity. *World J. Microbiol. Biotechnol.* **2015**, *6*, 865–873. [CrossRef]
26. Jahan, I.; Erci, F.; Isildak, I. Facile microwave-mediated green synthesis of non-toxic copper nanoparticles using *Citrus sinensis* aqueous fruit extract and their antibacterial potentials. *J. Drug Deliv. Sci. Technol.* **2021**, *61*, 102172. [CrossRef]
27. Cioffi, N.; Ditaranto, N.; Torsi, L.; Picca, R.A.; Sabbatini, L.; Valentini, A.; Novello, L.; Tantillo, G.; Bleve-Zacheo, T.; Zambonin, P.G. Analytical characterization of bioactive fluoropolymer ultra-thin coatings modified by copper nanoparticles. *Anal. Bioanal. Chem.* **2005**, *381*, 607–616. [CrossRef] [PubMed]
28. Vasiliev, G.; Kubo, A.-L.; Vija, H.; Kahru, A.; Bondar, D.; Karpichev, Y.; Bondarenko, O. Synergistic antibacterial effect of copper and silver nanoparticles and their mechanism of action. *Sci. Rep.* **2023**, *13*, 9202. [CrossRef]
29. Zhang, E.; Zhao, X.; Hu, J.; Wang, R.; Fu, S.; Qin, G. Antibacterial metals and alloys for potential biomedical implants. *Bioact. Mater.* **2021**, *6*, 2569–2612. [CrossRef] [PubMed]
30. Yin, S.; Liu, J.; Kang, Y.; Lin, Y.; Li, D.; Shao, L. Interactions of nanomaterials with ion channels and related mechanisms. *Br. J. Pharmacol.* **2019**, *176*, 3754–3774. [CrossRef] [PubMed]
31. Grace, M.; Chand, N.; Bajpai, S.K. Copper alginate-cotton cellulose (CACC) fibers with excellent antibacterial properties. *J. Eng. Fibers Fabr.* **2009**, *4*, 24–35. [CrossRef]
32. Jardón-Maximino, N.; Cadenas-Pliego, G.; Ávila-Orta, C.A.; Comparán-Padilla, V.E.; Lugo-Uribe, L.E.; Pérez-Alvarez, M.; Tavizón, S.F.; Santillán, G.d.J.S. Antimicrobial property of polypropylene composites and functionalized copper nanoparticles. *Polymers* **2021**, *13*, 1694. [CrossRef]
33. Mondal, A.; Mondal, N.K. Efficacy of bile juice mediated Cu MWCNT nanostructure, with respect to antibacterial and antibiofilm activity. *Mater. Lett.* **2023**, *335*, 133828. [CrossRef]
34. Longano, D.; Ditaranto, N.; Sabbatini, L.; Torsi, L.; Cioffi, N. Synthesis and antimicrobial activity of copper nanomaterials. *Nano-Antimicrob.* **2011**, *26*, 85–117. [CrossRef]
35. Torras, M.; Roig, A. Copper oxide nanocubes wrapping metals by microwave synthesis. *Cryst. Growth Des.* **2021**, *21*, 5027–5035. [CrossRef]
36. Osonga, F.J.; Eshun, G.; Kalra, S.; Yazgan, I.; Sakhaee, L.; Ontman, R.; Jiang, S.; Sadik, O.A. Influence of particle size and shapes on the antifungal activities of greener nanostructured copper against Penicillium italicum. *ACS Agric. Sci. Technol.* **2022**, *2*, 42–56. [CrossRef]
37. Mahmoodi, S.; Elmi, A.; Hallaj-Nezhadi, S. Copper nanoparticles as antibacterial agents. *J. Mol. Pharm. Org. Process. Res.* **2018**, *6*, 140. [CrossRef]
38. Chen, Z.; Meng, H.; Xing, G.; Chen, C.; Zhao, Y.; Jia, G.; Wang, T.; Yuan, H.; Ye, C.; Zhao, F.; et al. Acute toxicological effects of copper nanoparticles in vivo. *Toxicol. Lett.* **2006**, *163*, 109–120. [CrossRef] [PubMed]
39. Mehtar, S.; Wiid, I.; Todorov, S.D. The antimicrobial activity of copper and copper alloys against nosocomial pathogens and *Mycobacterium tuberculosis* isolated from healthcare facilities in the Western Cape: An in-vitro study. *J. Hosp. Infect.* **2008**, *68*, 45–51. [CrossRef] [PubMed]

40. Karakoti, A.S.; Hench, L.L.; Seal, S. The potential toxicity of nanomaterials—The role of surfaces. *J. Miner.* **2006**, *58*, 77–82. [CrossRef]
41. Aillón-García, P.; Parga-Landa, B.; Guillén-Grima, F. Effectiveness of copper as a preventive tool in health care facilities. A systematic review. *Am. J. Infect. Control* **2023**, *51*, 1038–1048. [CrossRef] [PubMed]
42. Ma, X.; Zhou, S.; Xu, X.; Du, Q. Copper-containing nanoparticles: Mechanism of antimicrobial effect and application in dentistry-a narrative review. *Front. Surg.* **2022**, *9*, 905892. [CrossRef] [PubMed]
43. Freedman, J.H.; Ciriolo, M.R.; Peisach, J. The role of glutathione in copper metabolism and toxicity. *J. Biol. Chem.* **1989**, *264*, 5598–5605. [CrossRef]
44. Ruparelia, J.P.; Chatterjee, A.K.; Duttagupta, S.P.; Mukherji, S. Strain specificity in antimicrobial activity of silver and copper nanoparticles. *Acta Biomat.* **2008**, *4*, 707–716. [CrossRef]
45. Hans, M.; Erbe, A.; Mathews, S.; Chen, Y.; Solioz, M.; Mücklich, F. Role of copper oxides in contact killing of bacteria. *Langmuir* **2013**, *29*, 16160–16166. [CrossRef]
46. Malaikozhundan, B.; Lakshmi, V.N.; Krishnamoorthi, R. Copper oxide nanoparticles using *Mentha spicata* leaves as antibacterial, antibiofilm, free radical scavenging agent and efficient photocatalyst to degrade methylene blue dyes. *Mater. Today Commun.* **2022**, *33*, 104348. [CrossRef]
47. Stoyanova, D.S. Antimicrobial Activity of Nanomaterials. Ph.D. Thesis, Sofia University St. Kliment Ohridski, Sofia, Bulgaria, 2018.
48. Fijan, S.; Cencič, A.; Turk, S.S. Hygiene monitoring of textiles used in the food industry. *Braz. J. Microbiol* **2006**, *37*, 356–361. [CrossRef]
49. Grace, M.; Bajpai, S.K.; Chand, N. Copper (II) ions and copper nanoparticles-loaded chemically modified cotton cellulose fibers with fair antibacterial properties. *J. Appl. Polym. Sci.* **2009**, *113*, 757–766. [CrossRef]
50. Perelshtein, I.; Applerot, G.; Perkas, N.; Wehrschuetz-Sigl, E.; Hasmann, A.; Gübitz, G.; Gedanken, A. CuO–cotton nanocomposite: Formation, morphology, and antibacterial activity. *Surf. Coat. Technol.* **2009**, *204*, 54–57. [CrossRef]
51. Toodehzaeim, M.H.; Zandi, H.; Meshkani, H.; Firouzabadi, A.H. The effect of CuO nanoparticles on antimicrobial effects and shear bond strength of orthodontic adhesives. *J. Dent.* **2018**, *19*, 1–5.
52. Noyce, J.O.; Michels, H.; Keevil, C.W. Potential use of copper surfaces to reduce survival of epidemic methicillin-resistant *Staphylococcus aureus* in the healthcare environment. *J. Hosp. Infect.* **2006**, *63*, 289–297. [CrossRef] [PubMed]
53. Michels, H.T.; Noyce, J.O.; Keevil, C.W. Effects of temperature and humidity on the efficacy of methicillin-resistant *Staphylococcus aureus* challenged antimicrobial materials containing silver and copper. *Appl. Microbiol.* **2009**, *49*, 191–195. [CrossRef] [PubMed]
54. Warnes, S.L.; Green, S.; Michels, H.T.; Keevil, C.W. Biocidal efficacy of copper alloys against pathogenic enterococci involves degradation of genomic and plasmid DNAs. *Appl. Environ. Microbiol.* **2010**, *76*, 5390–5401. [CrossRef]
55. Chalandar, H.E.; Ghorbani, H.R.; Attar, H.; Abolhasan, S. Antifungal effect of copper and copper oxide nanoparticles against Penicillium on orange fruit. *Alavi Biosci. Biotech. Res. Asia* **2017**, *14*, 279–284. [CrossRef]
56. Borkow, G.; Gabbay, J. Copper as a biocidal tool. *Curr. Med. Chem.* **2005**, *12*, 2163–2175. [CrossRef]
57. Angelov, O.; Stoyanova, D.; Ivanova, I.A. Antimicrobial effect of TiO_2 doped with Ag and Cu on *Escherichia coli* and *Pseudomonas putida*. In Proceedings of the INERA Conference "Vapor Phase Technologies for Metal Oxide and Carbon Nanostructures", Velingrad, Bulgaria, 6–8 July 2016. Available online: https://ui.adsabs.harvard.edu/abs/2016JPhCS.764a2014A/abstract (accessed on 10 December 2023).
58. Kim, K.H.; Yang, M.; Song, Y.; Kim, C.H.; Jung, Y.M.; Bae, N.H.; Chang, S.J.; Lee, S.J.; Kim, Y.T.; Choi, B.G.; et al. Touchable 3D hierarchically structured polyaniline nanoweb for capture and detection of pathogenic bacteria. *Nano Converg.* **2021**, *8*, 30–41. [CrossRef]
59. Maniprasad, P.; Santra, S. Novel copper (Cu) loaded core-shell silica nanoparticles with improved Cu bioavailability: Synthesis, characterization and study of antibacterial properties. *J. Biomed. Nanotechnol.* **2012**, *8*, 558–566. [CrossRef]
60. Stanić, V.; Dimitrijević, S.; Antić-Stanković, J.; Mitrić, M.; Jokić, B.; Plećaš, I.B.; Raičević, S. Synthesis, characterization and antimicrobial activity of copper and zinc doped hydroxyapatite nanopowders. *Appl. Surf. Sci.* **2010**, *256*, 6083–6089. [CrossRef]
61. Yaseen, M.; Farooq, S.; Khan, A.; Shah, N.; Shah, L.A.; Bibi, S.; Khan, I.U.; Ahmad, S. CuO-SiO_2 based nanocomposites: Synthesis, characterization, photocatalytic, antileishmanial, and antioxidant studies. *J. Chin. Chem. Soc.* **2022**, *69*, 1637–1653. [CrossRef]
62. Sunada, K.; Kikuchi, Y.; Hashimoto, K.; Fujishima, A. Bactericidal and detoxification effects of TiO_2 thin film photocatalysts. *Environ. Sci. Technol.* **1998**, *32*, 726–728. [CrossRef]
63. Mingmongkol, Y.; Trinh, D.T.T.; Phuinthiang, P.; Channei, D.; Ratananikom, K.; Nakaruk, A.; Khanitchaidecha, W. Enhanced photocatalytic and photokilling activities of Cu-doped TiO_2 nanoparticles. *Nanomaterials* **2022**, *12*, 1198. [CrossRef] [PubMed]
64. Paszkiewicz, M.; Gołąbiewska, A.; Rajski, L.; Kowal, E.; Sajdak, A.; Zaleska-Medynska, A. Synthesis and characterization of monometallic (Ag, Cu) and bimetallic Ag-Cu particles for antibacterial and antifungal applications. *J. Nanomater.* **2016**, *2016*, 2187940. [CrossRef]
65. Ameh, T.; Gibb, M.; Stevens, D.; Pradhan, S.H.; Braswell, E.; Sayes, C.M. Silver and copper nanoparticles induce oxidative stress in bacteria and mammalian cells. *Nanomaterials* **2022**, *12*, 2402. [CrossRef] [PubMed]
66. Pant, J.; Goudie, M.J.; Hopkins, S.P.; Brisbois, E.J.; Handa, H. Tunable nitric oxide release from S-nitroso-N-acetylpenicillamine via catalytic copper nanoparticles for biomedical applications. *ACS Appl. Mater. Interfaces* **2017**, *9*, 15254–15264. [CrossRef] [PubMed]
67. Crane, J.K. Metal nanoparticles in infection and immunity. *Immunol. Investig.* **2020**, *49*, 794–807. [CrossRef]
68. Fan, X.; Yahia, L.; Sacher, E. Antimicrobial properties of the Ag, Cu nanoparticle system. *Biology* **2021**, *10*, 137. [CrossRef]

69. Rolim, W.R.; Pieretti, J.C.; Renó, D.L.; Lima, B.A.; Nascimento, M.H.; Ambrosio, F.N.; Lombello, C.B.; Brocchi, M.; de Souza, A.C.S.; Seabra, A.B. Antimicrobial activity and cytotoxicity to tumor cells of nitric oxide donor and silver nanoparticles containing PVA/PEG films for topical applications. *ACS Appl. Mater. Interfaces* **2019**, *11*, 6589–6604. [CrossRef]
70. *EN ISO 14729:2001*; Ophthalmic Optics—Contact Lens Care Products—Microbiological Requirements and Test Methods for Products and Regimens for Hygienic Management of Contact Lenses. ISO: Geneva, Switzerland, 2001.
71. Mohan, R.; Shanmugharaj, A.M.; Sung Hun, R. An efficient growth of silver and copper nanoparticles on multiwalled carbon nanotube with enhanced antimicrobial activity. *J. Biomed. Mater. Res. B Appl. Biomater.* **2011**, *96*, 119–126. [CrossRef]
72. Datta, K.K.R.; Srinivasan, B.; Balaram, H.; Eswaramoorthy, M. Synthesis of agarose–metal/semiconductor nanoparticles having superior bacteriocidal activity and their simple conversion to metal–carbon composites. *J. Chem. Sci.* **2008**, *120*, 579–586. [CrossRef]
73. Heinlaan, M.; Ivask, A.; Blinova, I.; Dubourguier, H.C.; Kahru, A. Toxicity of nanosized and bulk ZnO, CuO and TiO_2 to bacteria *Vibrio fischeri* and crustaceans *Daphnia magna* and *Thamnocephalus platyurus*. *Chemosphere* **2008**, *71*, 1308–1316. [CrossRef]
74. Gurianov, Y.; Nakonechny, F.; Albo, Y.; Nisnevitch, M. Antibacterial composites of cuprous oxide nanoparticles and polyethylene. *Int. J. Mol. Sci.* **2019**, *20*, 439. [CrossRef]
75. Ditta, B.; Steele, A.; Liptrott, C.; Tobin, J.; Tyler, H.; Yates, M.; Sheel, W.; Foster, A. Photocatalytic antimicrobial activity of thin surface films of TiO_2, CuO, and TiO_2/CuO dual layers on *Escherichia coli* and bacteriophage T4. *Appl. Microbiol. Biotechnol.* **2008**, *79*, 127–133. [CrossRef]
76. Ivanova, I.A.; Pavlova, E.L.; Stoyanova, D.S.; Angelov, O.I. Antibacterial effect of TiO_2: Cu: Ag thin coatings on *Pseudomonas* strain measured by microbiological and ATP assays. *J. Basic Microbiol.* **2019**, *59*, 1165–1172. [CrossRef]
77. Shimabukuro, M. Antibacterial property and biocompatibility of silver, copper, and zinc in titanium dioxide layers incorporated by one-step micro-arc oxidation: A review. *Antibiotics* **2020**, *9*, 716. [CrossRef]
78. Ivanova, I.; Stoyanova, D.; Nenova, E.; Staneva, A.; Kostadinova, A. Antimicrobial and cytotoxic properties of metal and graphene nanomaterials (review). *J. Chem. Technol. Metall.* **2020**, *55*, 239–250.
79. Villapún, V.; Dover, L.; Cross, A.; González, S. Antibacterial metallic touch surfaces. *Materials* **2016**, *9*, 736. [CrossRef] [PubMed]
80. Leyland, N.S.; Podporska-Carroll, J.; Browne, J.; Hinder, S.J.; Quilty, B.; Pillai, S.C. Highly efficient F, Cu doped TiO_2 anti-bacterial visible light active photocatalytic coatings to combat hospital-acquired infections. *Sci. Rep.* **2016**, *6*, 24770. [CrossRef] [PubMed]
81. Rtimi, S.; Giannakis, S.; Sanjines, R.; Pulgarin, C.; Bensimon, M.; Kiwi, J. Insight on the photocatalytic bacterial inactivation by co-sputtered TiO_2-Cu in aerobic and anaerobic conditions. *Appl. Catal. B Environ.* **2016**, *182*, 277–285. [CrossRef]
82. Usman, M.S.; El Zowalaty, M.E.; Shameli, K.; Zainuddin, N.; Salama, M.; Ibrahim, N.A. Synthesis, characterization, and antimicrobial properties of copper nanoparticles. *Int. J. Nanomed.* **2013**, *8*, 4467–4479. [CrossRef]
83. Vanti, G.L.; Masaphy, S.; Kurjogi, M.; Chakrasali, S.; Nargund, V.B. Synthesis and application of chitosan-copper nanoparticles on damping off causing plant pathogenic fungi. *Int. J Biol. Macromol.* **2020**, *156*, 1387–1395. [CrossRef] [PubMed]
84. Qi, L.; Xu, Z.; Jiang, X.; Wang, M. Cytotoxic activities of chitosan nanoparticles and copper-loaded nanoparticles. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1397–1399. [CrossRef]
85. Li, X.; Xu, H.; Zhe-Sheng, C.; Chen, G. Biosynthesis of nanoparticles by microorganisms and their applications. *J. Nanomater.* **2011**, *2011*, 270974. [CrossRef]
86. Hongfeng, Z.; El-Kott, A.; Ahmed, A.E.; Khames, A. Synthesis of chitosan-stabilized copper nanoparticles (CS-Cu NPs): Its catalytic activity for C-N and C-O cross-coupling reactions and treatment of bladder cancer. *Arab. J. Chem.* **2021**, *14*, 103259. [CrossRef]
87. De La Torre-Roche, R.; Cantu, J.; Tamez, C.; Zuverza-Mena, N.; Hamdi, H.; Adisa, I.O.; Elmer, W.; Gardea-Torresdey, J.; White, J.C. Seed biofortification by engineered nanomaterials: A pathway to alleviate malnutrition? *J. Agric. Food Chem.* **2020**, *68*, 12189–12202. [CrossRef] [PubMed]
88. Hejazy, M.; Koohi, M.; Bassiri, M.P.A.; Najafi, D. Toxicity of manufactured copper nanoparticles—A review. *Nanomed. Res. J.* **2018**, *3*, 1–9. [CrossRef]
89. Naz, S.; Gul, A.; Zia, M. Toxicity of copper oxide nanoparticles: A review study. *IET Nanobiotechnology* **2020**, *14*, 1–13. [CrossRef] [PubMed]
90. Mathew, S.; Ganguly, P.; Rhatigan, S.; Kumaravel, V.; Byrne, C.; Hinder, S.J.; Bartlett, J.; Nolan, M.; Pillai, S.C. Cu-doped TiO_2: Visible light assisted photocatalytic antimicrobial activity. *Appl. Sci.* **2018**, *8*, 2067. [CrossRef]
91. Qin, Q.; Li, J.; Wang, J. Antibacterial activity comparison of three metal oxide nanoparticles and their dissolved metal ions. *Water Environ. Res.* **2017**, *89*, 378–383. [CrossRef]
92. Sandle, T. *Risk Management Library Volume 4: Practical Approaches to Risk Assessment and Management Problem Solving: Tips and Case Studies*; DHI Publishing, LLC: River Grove, IL, USA, 2018.
93. Salgado, C.D.; Sepkowitz, K.A.; John, J.F.; Cantey, J.R.; Attaway, H.H.; Freeman, K.D.; Sharpe, P.A.; Michels, H.T.; Schmidt, M.G. Copper surfaces reduce the rate of healthcare-acquired infections in the intensive care unit. *Infect. Control Hosp. Epidemiol.* **2013**, *34*, 479–486. [CrossRef] [PubMed]
94. Santo, C.E.; Lam, E.W.; Elowsky, C.G.; Quaranta, D.; Domaille, D.W.; Chang, C.J.; Grass, G. Bacterial killing by dry metallic copper surfaces. *Appl. Environ. Microbiol.* **2011**, *77*, 794–802. [CrossRef]
95. Efstathiou, G.; Papastavrou, E.; Raftopoulos, V.; Merkouris, A. Factors influencing nurses' compliance with standard precautions in order to avoid occupational exposure to microorganisms: A focus group study. *BMC Nurs.* **2011**, *10*, 1. [CrossRef]

96. Khan, H.A.; Baig, F.K.; Mehboob, R. Nosocomial infections: Epidemiology, prevention, control and surveillance. *Asian Pac. J. Trop. Biomed.* **2017**, *7*, 478–482. [CrossRef]
97. Abraham, J.; Dowling, K.; Florentine, S. Can copper products and surfaces reduce the spread of infectious microorganisms and hospital-acquired infections? *Materials* **2021**, *14*, 3444. [CrossRef] [PubMed]
98. Montero, D.A.; Arellano, C.; Pardo, M.; Vera, R.; Gálvez, R.; Cifuentes, M.; Berasain, M.A.; Gómez, M.; Ramírez, C.; Vidal, R.M. Antimicrobial properties of a novel copper-based composite coating with potential for use in healthcare facilities. *Antimicrob. Resist. Infect. Control* **2019**, *8*, 3. [CrossRef] [PubMed]
99. Schmidt, M.; Bréchot, N.; Hariri, S.; Guiguet, M.; Luyt, C.E.; Makri, R.; Leprince, P.; Trouillet, J.L.; Pavie, A.; Chastre, J.; et al. Nosocomial infections in adult cardiogenic shock patients supported by venoarterial extracorporeal membrane oxygenation. *Clin. Infect. Dis.* **2012**, *55*, 1633–1641. [CrossRef] [PubMed]
100. Pontin, K.P.; Borges, K.A.; Furian, T.Q.; Carvalho, D.; Wilsmann, D.E.; Cardoso, H.R.P.; Alves, A.K.; Chitolina, G.Z.; Salle, C.T.P.; de Souza Moraes, H.L.; et al. Antimicrobial activity of copper surfaces against biofilm formation by *Salmonella enteritidis* and its potential application in the poultry industry. *Food Microbiol.* **2021**, *94*, 103645. [CrossRef] [PubMed]
101. DeAlba-Montero, I.; Guajardo-Pacheco, J.; Morales-Sánchez, E.; Araujo-Martínez, R.; Loredo-Becerra, G.M.; Martínez-Castañón, G.A.; Ruiz, F.; Compeán Jasso, M.E. Antimicrobial properties of copper nanoparticles and amino acid chelated copper nanoparticles produced by using a soya extract. *Bioinorg. Chem. Appl.* **2017**, *2017*, 1064918. [CrossRef]
102. Mohindru, J.; Garg, U. Green synthesis of copper nanoparticles using tea leaf extract. *Int. J. Eng. Sci. Res. Technol.* **2017**, *6*, 307–311. [CrossRef]
103. Atiya, M.A.; Hassan, A.K.; Kadhim, F.Q. Green Synthesis of copper nanoparticles using tea leaves extract to remove ciprofloxacin (CIP) from aqueous media. *Iraqi J. Sci.* **2021**, *62*, 2832–2854. [CrossRef]
104. Khaldari, I.; Naghavi, M.R.; Motamedi, E. Synthesis of green and pure copper oxide nanoparticles using two plant resources via solid-state route and their phytotoxicity assessment. *RSC Adv.* **2021**, *11*, 3346–3353. [CrossRef]
105. Sutradhar, P.; Saha, M.; Maiti, D. Microwave synthesis of copper oxide nanoparticles using tea leaf and coffee powder extracts and its antibacterial activity. *J. Nanostruct. Chem.* **2014**, *4*, 86. [CrossRef]