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Study of Biocidal Activity of Copper: A Review

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ABSTRACT

Copper ions, either alone or in copper complexes, have been used to disinfect liquids, solids and human tissue for centuries. Today copper is used as a water purifier, algaecide, fungicide, nematocide, molluscicide as well as an anti-bacterial and anti-fouling agent. Copper also displays potent anti-viral activity. We have explained (i) the biocidal properties of copper; (ii) the possible mechanisms by which copper is toxic to microorganisms; and (iii) the systems by which many microorganisms resist high concentrations of heavy metals, with an emphasis on copper. Health care-associated infections (HAIs) are a global problem associated with significant morbidity and mortality. Controlling the spread of antimicrobial-resistant bacteria is a major public health challenge, and antimicrobial resistance has become one of the most important global problems in current times. The antimicrobial effect of copper has been known for centuries, and ongoing research is being conducted on the use of copper-coated hard and soft surfaces for reduction of microbial contamination and, subsequently, reduction of HAIs.

KEYWORDS: *copper, biocidal, fungi, health, antimicrobial, heavy metals, anti-fouling, contamination*

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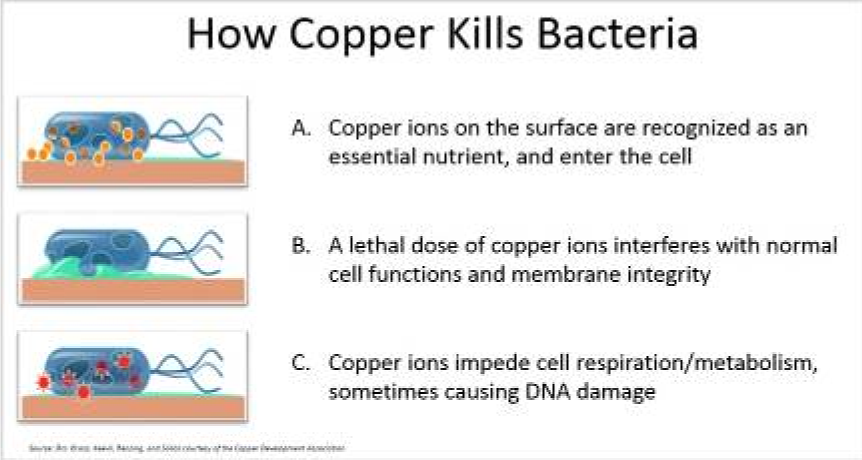
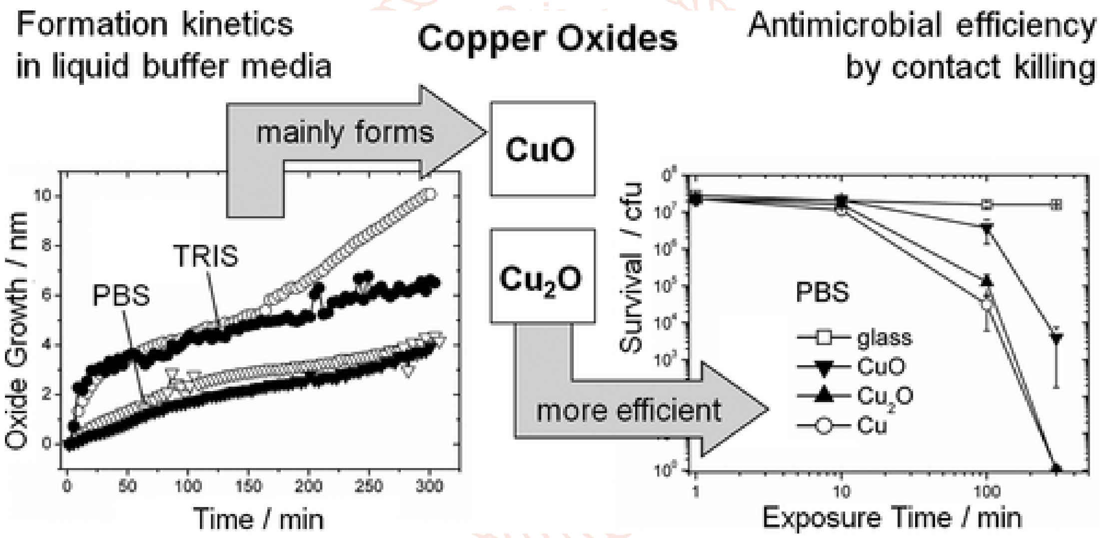
INTRODUCTION

The bacteriostatic effect of copper was noted by Dr. Phyllis J. Kuhn, who was involved in the training of housekeeping and maintenance personnel at the Hamot Medical Center in Pennsylvania. To heighten their awareness of modes of infection, the students were given blood agar plates and instructions on their use. The students returned with bacterial cultures from such diverse sources as toilet bowl water (remarkably clean), salad from the employees' cafeteria (heavily colonized), and doorknobs. Brass (an alloy of 67% copper and 33% zinc) doorknob cultures showed sparse streptococcal and staphylococcal growth while stainless steel (about 88% iron and 12% chromium) doorknob cultures showed heavy growth of gram-positive organisms and an array of gram-negative organisms.[1,2] Current research is focused on the antimicrobial properties of copper to demonstrate its benefit and elucidate its mechanisms of action. Current applications of copper use are extensive and range from construction sites to healthcare infection prevention in hospitals despite the lack of understanding of the exact antimicrobial mode(s) of action and possible limitations. The antibacterial effect of copper over time was evaluated in the four most prevalent strains [coagulase-negative *Staphylococci* (CNS) (MT-163), *E. coli* (Al-563), *S. aureus* (MT-359), and *S. uberis* (MT-360)] isolated from milk with clinical bovine mastitis. Bioactive copper nanomaterials are an emerging class of nano-antimicrobials providing complimentary effects and characteristics, as compared to other nano-sized metals, such as silver or zinc oxide nanoparticles. Copper nano-antimicrobials are reviewed and classified firstly as a function of the preparation methods, and secondly as a function of the target microorganism used for testing their antimicrobial activity. [3,4]

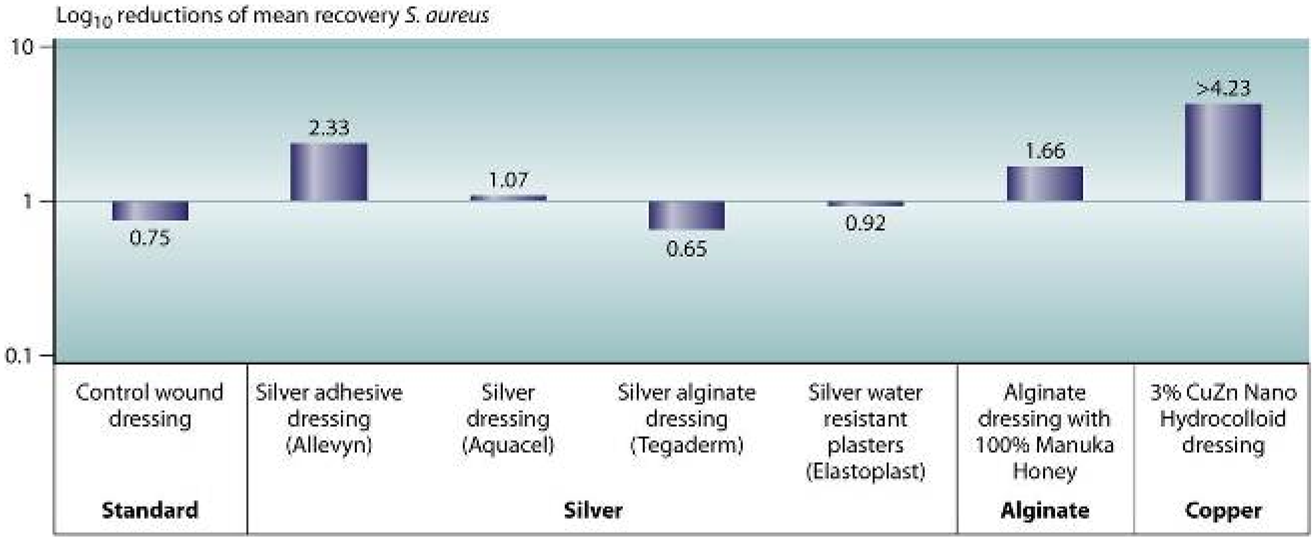


The antimicrobial activity of copper-based nanostructures depends on the microbial species and on the experimental set-up. As a consequence, in this chapter details are provided on methods, as well as on experimental details such as contact time, microorganism strain, concentration of the interacting species, etc.[5,6] Copper alloy surfaces have intrinsic properties to destroy a wide range of microorganisms. In the interest of protecting public health, especially in healthcare environments with their susceptible patient populations, an abundance of antimicrobial efficacy studies have been conducted in the past ten years regarding copper's efficacy to destroy *E. coli* O157:H7, methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus*, *Clostridium difficile*, influenza A virus, adenovirus, and fungi.



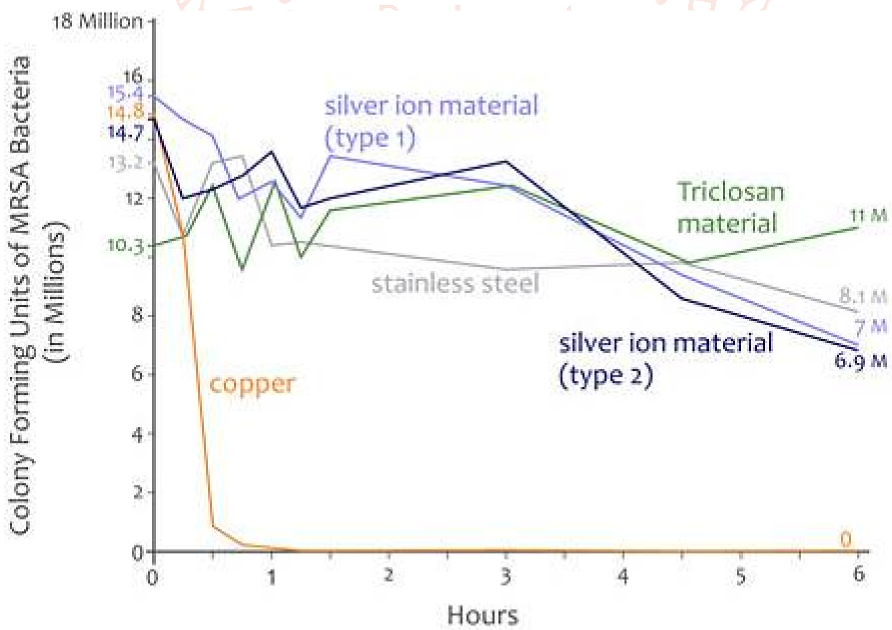
Cu Nps solutions were prepared by chemical reduction method from chemicals and materials including copper (II) chloride dehydrate ($CuCl_2 \cdot 2H_2O$, Merck, Germany, 99.99%), cetyltrimethylammonium bromide [$(C_{16}H_{33})N(CH_3)_3Br$, CTAB, India, 99.99%], deionized (DI) water from Thermo Scientific Equipment, ascorbic acid ($C_6H_8O_6$, India, 99.99%), D-glucose ($C_6H_{12}O_6$, Sigma-Aldrich, 99.5%), [7,8] chloramphenicol ($C_{11}H_{12}Cl_2N_2O_5$), double-distilled water (Vietnam), and the TCBS agar (Difco, USA). the inhibition efficiency of Cu Nps was good in the *in vitro* condition. However, the inhibition efficiency of Cu Nps increases according to the concentration used. In a 3-day incubation, Cu Nps solutions inhibited 43% of growth of fungi of the samples at the concentration of 300 ppm and 380 ppm. Meanwhile, Cu Nps solution could inhibit 67.38% of the fungal growth at 450 ppm concentration after being incubated for 3 days and reaches 93.98% if incubated for 9 days. At this time the results show that inhibition efficiency of Cu Nps solution went up significantly due to 450 ppm concentration dish; the fungi were inhibited intensively and no longer grew in a 3-day incubation. In contrast, the fungi in the reference sample still grew normally and their diameter increased constantly.

Copper oxide impregnated socks prevent and treat fungal foot infections (athlete's foot). Wound dressings containing copper oxide reduce the dressing and wound contamination. Application of wound dressings containing copper oxide to wounds inflicted in genetically engineered diabetic mice resulted in increased gene and in situ upregulation of pro-angiogenic factors (e.g., placental growth factor, HIF-1a and VEGF), increased blood vessel formation, and enhanced wound closure, as compared to control dressings (without copper) or commercial wound dressings containing silver. Importantly, they enhance and allow wound repair, especially of diabetic ulcers in which conventional treatment modalities fail to close the wounds.[9,10]



Discussion

Three formulations of copper salts or copper complexes encapsulated by different kinds of polymers were locally prepared in the Polymers and Pigments Department. The biological activity of these compounds were studied against various types of fungal strains. The dose and the rate of leaching of copper ions were also studied. They were significantly controlled by the type of the polymer film used and the solubility in the medium. The effective doses of the biocide were (0.1- 0.2 mg/ml). The different kinds of used polymers improved the tenacity of the fungicides on the leaf surfaces and improved the dispersion of copper salt suspension. The results provided laboratory support for the concept that the polymers containing chemically bound biocides were useful for controlling microorganisms growth. In field application, the role of polymer film is obviously clear in the protection of most copper salts or complexes that can be used in rainy and windy places to obtain both economic and environmental advantages. The copper uptake by fungal strains were studied to determine their difference in behavior to the biocidal activity of these compounds. The uptake strategy was examined by Transmission Electron Microscope (TEM). In addition, the cytological studies on and in cucumber leaves showed an efficient intracellular diffusion of copper ions.[11,12]



The synthesis of metal nanoparticles is an emerging area of advanced research and technology with potential application in plant protection. In the current study, with an eco-friendly approach, a convenient method was adopted, where copper nanoparticles are biosynthesised extracellularly by using *Streptomyces griseus*. Further, the existence of nanoparticles was confirmed by UV–visible spectroscopy, transmission electron microscopy, X-ray diffraction analysis and Fourier transform infrared spectroscopy characterisation. We assessed the field effectiveness of copper nanoparticles through soil application in *P. hypolateritia* infested tea plants. In response to seven different treatments, carbendazim exhibited superior control followed by nanocopper at 2.5 ppm dosage. However, maximum leaf yield was observed in plants treated with nanocopper. In addition, nanocopper-treated plants showed improved soil macronutrients considerably when compared to bulk copper and carbendazim treated plants. In addition, there was trivial variation in population dynamics of microbes noted in plants treated with nanocopper. These encouraging results confirmed that nanocopper could act as an efficient novel fungicide which may be used for the management of red root-rot disease in tea plantations.

Copper soaps are used as fungicides, bacteriosides, herbicides and insecticides. Copper complexes including heterocyclic compounds have attracted our attention in a magnificent way because of its utility in catalysis and biological functions. Their mechanism of synthesis, characterization and structural insight, are crucial for comprehending the criteria of the bonding and electronic interactions between the proximate metal center and chelating atoms. But still, there is a need to explore some of more biological properties for their wide applicability and significant usage in multiple fields because it is an untapped area with potentially tremendous value.[13]

Copper pesticides are a group of many different compounds that have some form of copper in common as the active ingredient. These compounds have protectant activity against several bacterial and fungal diseases. Although copper pesticides are one of the oldest class of fungicides (FRAC group M1), they are still used for management of many different diseases today

A combination of broad spectrum of activity, ability to withstand frequent wet weather events and inexpensive cost makes this group of compounds valuable in pest management programs. This overview of copper-based pesticides will cover Bordeaux mixture, copper sulfate, along with many other forms of copper and resistance of some bacterial pathogens to these materials.

Bordeaux mixture, made by adding copper sulfate and calcium hydroxide to water, was one of the first fungicides ever used. Millardet, a French viticulturist during the mid-1800s, noticed less grape downy mildew on vines close to the road while walking through a vineyard one day. Bordeaux has many positive and negative features. It is a highly effective bactericide and fungicide that is used to manage several plant diseases. The material sticks to and remains active on plant surfaces even during typical wet PNW winters. Generally it is used as a dormant spray because it may burn young juvenile tissues. The ingredients must be mixed in the right order and with mechanical agitation of the tank to avoid the formation of a sprayer clogging precipitate. Bordeaux cannot be mixed ahead of use because it deteriorates on standing.[14,15]

Many other copper-based pesticides have been developed to capture the positive weathering and disease control features of Bordeaux without the challenges of preparing the material properly. Copper-based active ingredients in other products include copper ammonium complex (Copper Count-N), copper hydroxide (Champion, Kocide, Nu-Cop, etc.), copper oxide (Nordox), copper oxychloride, (C-O-C-S), and copper sulfate (Cuprofix Disperss, many others).

The active ingredient in all copper-based formulations is the positively charged copper ion (Cu^{+2}). Many organisms are sensitive to very small amounts of copper ion, such as bacteria and fungi but especially aquatic organisms such as algae or water molds (including pathogens like downy mildews). Copper-based products have broad-spectrum activity against microorganisms due to copper's interaction with nucleic acids, interference with energy transport, and disruption of enzyme activity and integrity of cell membranes.

The same small amounts of copper are not toxic to plants or humans. Copper is important for the formation of red blood cells, activity of antioxidant enzymes and assists with the formation and maintenance of connective tissues in the human body

The red material cuprous oxide was first used as a seed treatment and later as a foliar fungicide. Formulated as Nordox the label allows application to a wide variety of crops for management of many different diseases. Cuprous oxide also has similar precautions as the fixed copper sulfates with pH and copper sensitive crops to prevent phytotoxicity. Rarely tested in the PNW, but has been used to significantly enhance pea emergence as a seed treatment. [16,17]

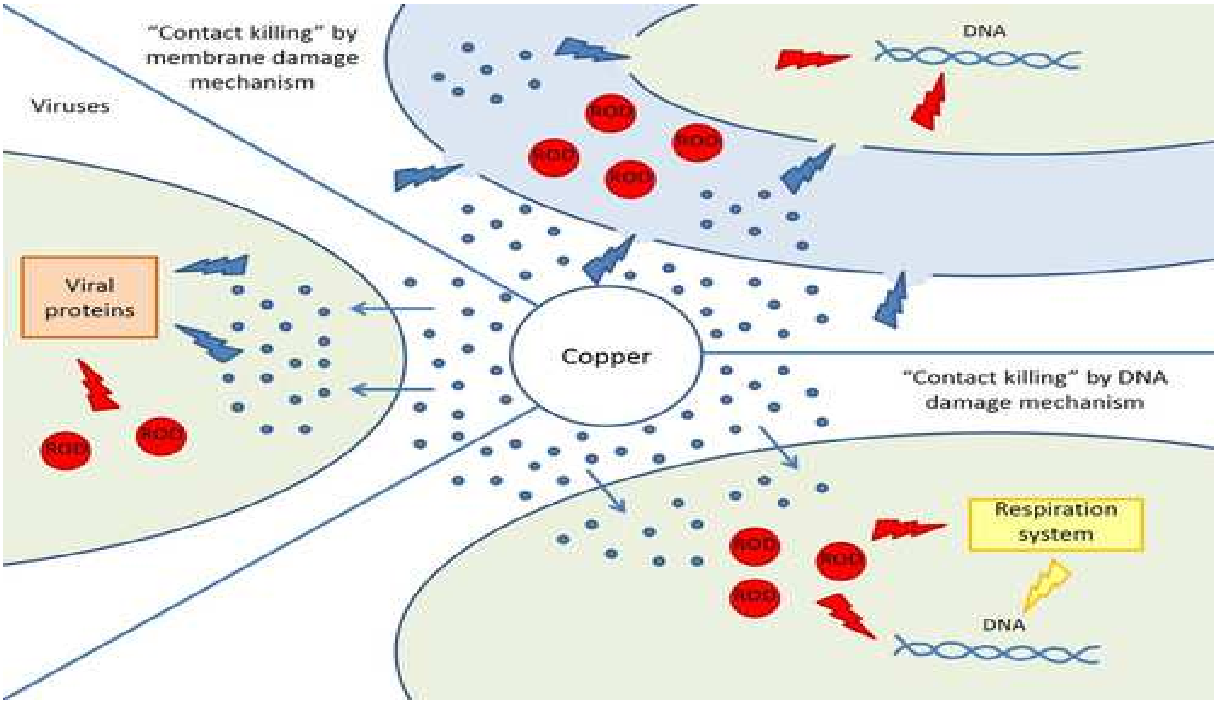
Results

Copper mixed with naturally occurring fatty acids forms copper salt of fatty acids, technically known as soap with an overall lower concentration of copper. Cueva contains copper octanoate, which is a blue material that can be used in the organic production of many crops. The lower copper ion release helped reduce phytotoxicity (russeting) in fire blight control trials in semi-arid Washington but have shown some risk of russeting in wetter areas of Oregon and California. West coast trials for management of spinach downy mildew, grape powdery mildew, or apple scab averaged about 50% control with variable results from year to year. Cueva was not effective against eastern filbert blight while other copper products generally resulted in good control.

Copper has potent biocidal properties. Copper ions, either alone or in copper complexes, have been used for centuries to disinfect liquids, solids and human tissue. Copper plays a key role in angiogenesis and in the expression and stabilization of extracellular skin proteins. Copper also exhibits broad biocidal properties. Introducing copper into a wound dressing would not only reduce the risk of wound and dressing contamination, but would also stimulate wound repair. To test this hypothesis, non-stick dressings composed of a highly absorbent internal mesh fabric and an external non-woven fabric were fabricated, and each was impregnated with ~2.65% (weight/weight) copper oxide particles. The application to wounds inflicted in genetically engineered diabetic mice resulted in increased gene and *in-situ* upregulation of proangiogenic factors, increased blood vessel formation, and enhanced wound closure. Studies demonstrate the high broad-spectrum biocidal efficacy and safety of wound dressings containing copper oxide, as demonstrated on skin and open wounds in animal models. These results further support the need to explore the potential of copper oxide containing wound dressings to enhance the wound healing process.

Extensive laboratory investigations have been carried out to investigate the biocidal activity of copper incorporated into contact surfaces and when impregnated into textiles and liquids. A limited number of clinical trials have been performed, which, although promising, leave significant questions unanswered. In particular there is a lack of consensus on minimum percentage copper alloys required for effectiveness, the impact of organic soiling on the biocidal effect of copper, and the best approach to routine cleaning of such surfaces. Limited information is available on the ability of copper surfaces to eradicate spores of *Clostridium difficile*.

With the emergence of antibiotic resistance, the interest for antimicrobial agents has recently increased again in public health. Copper was recognized in 2008 by the United States Environmental Protection Agency (EPA) as the first metallic antimicrobial agent. This led to many investigations of the various properties of copper as an antibacterial, antifungal and antiviral agent. [18]



'Contact killing' is initiated by the dissolved copper ions released from the copper surfaces by the culture medium and causing cell alterations

When copper concentration increases, the CusRS-like two-component system detects the high periplasmic copper amounts, triggers transcriptional activation of *cusRS* gene, which subsequently leads to the export of copper to the extracellular compartment. In parallel, the one-component CueR-like system recognizes high cytoplasmic copper concentrations and triggers transcriptional activation of copper resistance genes, with or without operon organization, for example, MCO, chaperone and copper-ATPase export [19]

Conclusions

It is confirmed that copper is a self-sanitising metal, acting on human pathogens in a way that does not let them survive exposure to copper or copper alloy surfaces for any reasonable length of time. This property is not seen with other common surface materials such as stainless steel, aluminium, and plastic which is a cause for some concern in the current pandemic environment. Regarding the efficacy of copper surfaces, testing in an independent microbiology laboratory has led to 300 various copper surfaces being registered with the United States Environmental Protection Agency (USEPA) in 2008. The registration includes the following statement: "When cleaned regularly, the antimicrobial copper alloy surface kills greater than 99.9% of bacteria within two hours and continues to kill more than 99% of bacteria even after repeated contamination". This claim acknowledges that copper and its alloys brass and bronze can kill potentially deadly bacteria, and sometime later, it was further understood that copper nanoparticles (Cu-NPs) and laser textured copper also show enhanced antimicrobial activity .[20]

The transmission of microbial pathogens through touching contaminated surfaces is always a significant and concerning problem for public health authorities. Studies have shown that the use of disinfecting methods to reduce the accumulation and transmission of the bioburden, although important, is not completely successful. This paper has argued that the modification of fomites by providing pure copper, copper alloys, and copperimpregnated products on frequent touch surfaces in the health and food industries and public places may make a considerable difference to the community and individual health outcomes. Research and development in this area of touch surfaces have lagged for some years because of the previous wide availability of effective antibiotics, but serious problems have emerged as a result of new antibiotic-resistant pathogens, plus the emergence of hitherto unknown strains such as SARS-CoV-2. The adage "prevention is better than cure" is widely agreed to be the best advice to follow from a public health perspective. Once an infection occurs and disease manifests in the body, notwithstanding the fact that there are remarkable possibilities for treatment in the healthcare environment, avoidance of severe consequences cannot always be guaranteed. This is particularly so in a situation like COVID-19, especially when patients are aged and have many types of comorbidities. In addition, even whilst treatment may be successful, the trauma may create lasting physical and mental issues, time is lost away from work and studies, and significant losses of savings can occur. Therefore, preventing the catching of an infection and avoiding the subsequent disease is arguably the best option to maintain health and well-being. From this perspective, we suggest that copper products and the installation of copper surfaces in hospitals and other healthcare facilities, food industries, public places, and public transport have a significant role in fostering community health by infection reduction and prevention. Communities are currently practicing a range of infection control procedures during this time of the COVID-19 pandemic. Hand hygiene, regular surface cleaning with disinfectants, applications of UV radiation, and infusion of hydrogen peroxide mists have all been investigated. However, many of these methods are not practical for large public gathering places and on public transport, and it is here that the effect of copper will be advantageous as it has continuing self-sanitising properties. Since copper products and surfaces act as a reducer or barrier to touch-transferred infections, the use of copper products and the installation of copper or copper alloy surfaces in healthcare facilities, public places, and public transport may reduce or avoid many of the current and upcoming infectious diseases [21]

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