COMMUNICATION

Nanostructured Copper Surface Kills ESKAPE Pathogens and Viruses in Minutes**

Guangshun Yi*,[a] Siti Nurhanna Riduan,[a] Arunmozhiarasi Armugam,[a] Jin Ting Ong,[b] Pei Yun Hon,[b] Mohammad Yazid Abdad,[b] Shawn Vasoo,[b] Brenda Ang,[b] and Yugen Zhang*[a]

[a] Dr. G. Yi, Dr. Y.G. Zhang, Dr. S. N. Riduan, Dr. A. Armugam
Institute of Bioengineering and Bioimaging,
31 Biopolis Way, The Nanos, Singapore 138669
E-mail: gsyi@ibb.a-star.edu.sg; ygzhang@ibb.a-star.edu.sg

[b] J. T. Ong, P. Y. Hon, Dr. M. Y. Abdad, Dr. S. Vasoo, Dr. B. Ang,
National Centre for Infectious Diseases, 16 Jalan Tan Tock Seng, Singapore 308442, and
Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433

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Abstract: *In the search for a fast contact-killing antimicrobial surface to break the transmission pathway of lethal pathogens, nanostructured copper surfaces were found to exhibit the desired antimicrobial properties. Compared with plain copper, these nanostructured copper surfaces with $Cu(OH)_2$ nano-sword or CuO nano-foam were found to completely eliminate pathogens at a fast rate, including clinically isolated drug resistant species. Additionally these nanostructured copper surfaces demonstrated potential antiviral properties when assessed against bacteriophages, as a viral surrogate, and murine hepatitis virus, a surrogate for SARS-CoV-2. The multiple modes of killing, physical killing and copper ion mediated killing contribute to the superior and fast kinetics of antimicrobial action against common microbes, and ESKAPE pathogens. Prototypes for air and water cleaning with current nanostructured copper surface have also been demonstrated.*

The onset of Coronavirus Disease 2019 (COVID-19) since early 2020 resulting in a global pandemic has raised urgent, pertinent issues on public health.[1] Breaking the virus transmission pathway has become a key strategy in containing the spread of the disease. While aerosols are the primary route of transmission, fomite transmission may play a role in spread of COVID-19 and other respiratory and enteric viruses.[2-4] It was reported that the SARS-CoV-2 virus can survive upto 28 days at 20 °C on common surfaces such as glass, stainless steel and both paper and polymer banknotes.[5] Aside from viruses, other lethal pathogens such as bacteria and fungi are also frequently transmitted via surface contact and contaminated water, or airborne transmission.[6] Specifically, ESKAPE pathogens which include six pathogens with growing multidrug resistance and virulence: *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter spp*., cause majority of nosocomial infections regardless of the biocidal action of antimicrobial agents.[4b] Therefore disinfection of surfaces and minimising contamination with viruses and ESKAPE pathodens is important, and may play a key role in diminishing transmission of disease, especially in high-traffic areas such as hospitals,[7] classrooms, mass transportation vehicles etc. [8]

In our evaluation of materials that can overcome lethal pathogens, copper merits attention.[9-10] As a natural antimicrobial material, copper and its alloys have been used as disinfectant agents for many centuries, even before when the concept of microbes became understood in the nineteenth century.[11] Copper and copper alloy touch surfaces have been shown to be 'cidal' against a wide range of microorganisms.[12] In 2008, the EPA officially recognized copper and its alloys as the first effective metallic antimicrobial agent.[13] The registration allowed the registrant, the Copper Development Association (CDA), to market these products with a claim that copper, when used in accordance with the label, "kills 99.9% of bacteria within two hours".[13-14] In comparison, these microbes can survive several days to weeks on stainless steel surfaces.[12, 15]

To break pathogen transmission over surface contact or airborne transmission, the rapid killing of microbes is crucial. Although copper surfaces can kill 99.9% (3 log reduction) of microorganisms in 2 hours, however, within these 2 hours, multifold transmission may have already occurred. Swift disinfection is the key factor in controlling transmission.

In other recent progress, nano-patterned surfaces as another antimicrobial surfaces has caught our attention. Naturally occurring surfaces such as cicada wings possessed nanopillared array; upon contact, bacteria will be killed by physical rupture.[16-17] The killing mechanism is purely based on physical structure, regardless of chemical composition.[18-21] Inspired by this concept, artificial nanostructured surfaces have been synthesized [22-23] and exhibited good antimicrobial properties against common pathogens.[20, 24-31]

With these two concepts in mind, we hypothesize that if we can grow copper-based nanostructures on copper, the intrinsic killing property, reinforced by the newly-added physical structure effect, would significantly enhance antimicrobial properties and accelerate disinfection.

In this paper, we successfully grew $Cu(OH)_2$ nano-sword and CuO nano-foam on copper surfaces. It was found that these nanostructure-coated copper surfaces kill microbes much faster than plain copper surfaces. It killed all *Escherichia coli* introduced on the surface within 10 min, in comparison with a 3 hours timepoint for plain copper surfaces under the same test conditions. We have also synthesized antimicrobial filter prototype with nano-structured copper surfaces and exhibited good air cleaning and water disinfection performance.

In our preliminary experiments, nano-patterns on copper substrate was prepared by treatment of copper foil in a $(NH_4)_2S_2O_8$ and NaOH mixture solution at room temperature, based on a method previously reported by Zhang et al.[32] As shown in Figure 1, when copper foil was treated with a low concentration of solution for 15 min, a nano-sword array was grown. The nano-sword array was aligned upright against the substrate and covered the whole area of the copper surface in a compact fashion. Each sword is 5-7 µm in length with an open and sharp tip of <100 nm diameter. The structure of the nano-sword was confirmed as $Cu(OH)_2$ with orthorhombic phase (JCPDS Card No. 13-0420) by X-ray diffraction (XRD).[32] In contrast, when the copper foil was treated with a highly concentrated solution of $(NH_4)_2S_2O_8$ and NaOH at ambient temperature for 30 min, foam-like structures was formed on the Cu surface. The structure was determined to be monoclinic symmetry of CuO on copper (JCPDS Card No. 48-1548).[33]

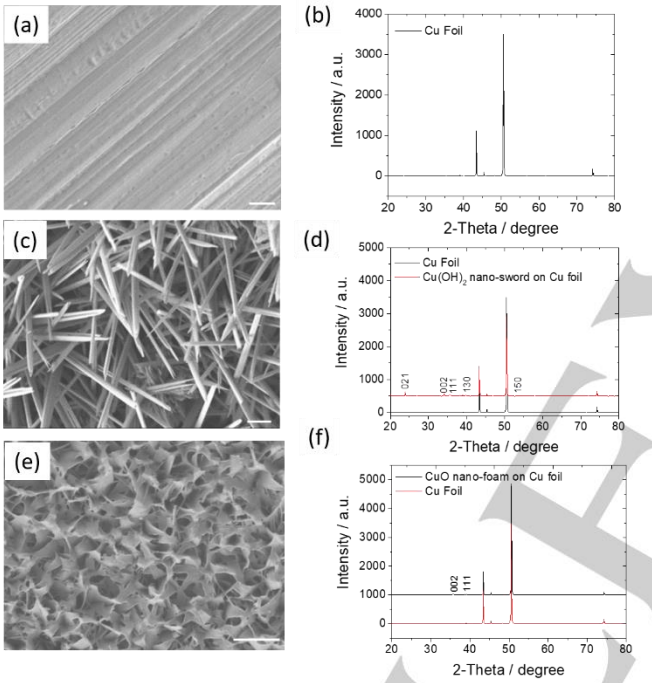

Figure 1. SEM images of (a) Cu foil, (c) $Cu(OH)_2$ nano-sword growing on Cu foil, and (e) CuO nano-foam growing on Cu foil. XRD confirmed the respective structures (b,d,f). Bar = 1 µM

The antimicrobial property of the as-prepared surfaces were evaluated using the JIS Z 2801/ISO 22196 method,[34] as shown in Figure 2. When tested with *E. coli* (representing Gram negative bacteria) and *S. aureus* (Gram positive bacteria), no colonies (6 log reduction) were found on $Cu(OH)_2$ nano-sword surface after 1 hour incubation. In comparison, CuO nano-foam surfaces only effected 1 to 2 log reduction and no killing effect was observed for Cu foil. Complete clearing of bacteria was only achieved after 3 and 24 hours for CuO and Cu foil surfaces, respectively. For fungal species such as *C. albicans*, it was observed that cells are still viable after 3 hours. However, after 24 hours, no colonies were observed on $Cu(OH)_2$ and CuO nano-foam surfaces, but *C. albicans* was still viable on the copper foil surface (Fig 2 (c)).

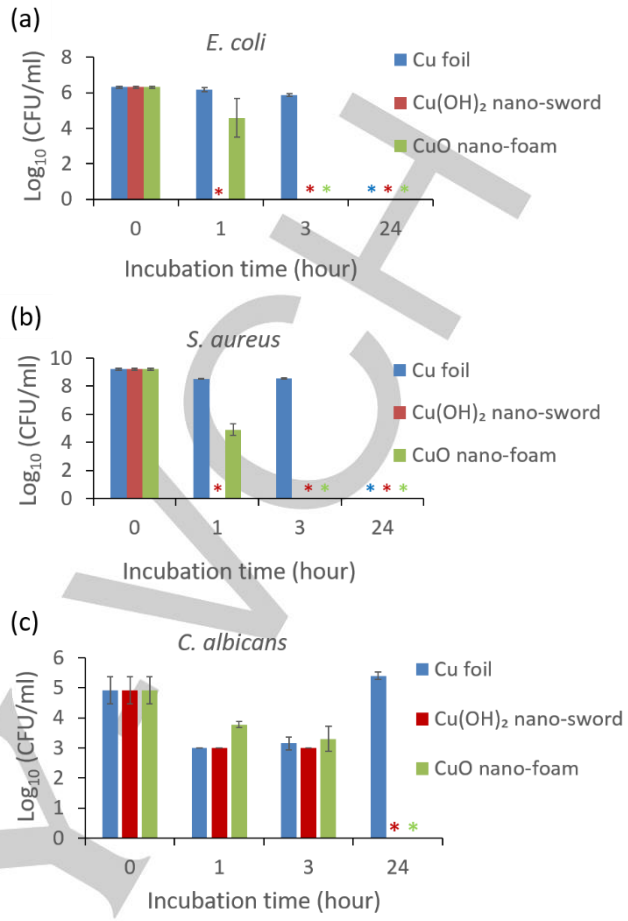

Figure 2. Antimicrobial properties of copper foil, $Cu(OH)_2$ nano-sword array surface, and CuO nano-foam surface for different type of microbe of (a) *E. coli, (b) S. aureus, and (c) C. albicans.* The evaluation method is JIS Z 2801/ISO 22196 method. * indicates no colonies was found. Data are representative of three independent experiments and values are expressed in mean ± SD.

From Figure 2, it is clear that the killing efficacy of the surfaces are in the order of $Cu(OH)_2$ nano-sword > CuO nano-foam > Cu foil, which suggests that the sharper the surface, the better the killing efficacy. However, for copper-based antimicrobial materials, it is known that the primary mode of killing is via contact; where the copper surfaces induced the degradation of membrane and genotoxicity.[35-36] The release of copper ions might have played an additional critical role in its antimicrobial action, especially when the chemical composition of the three surfaces are different, and the good killing property may be due to the surface composition instead of the structure effect. To investigate this, we immersed the three surfaces of copper foil, $Cu(OH)_2$ nano-sword and CuO nano-foam in Tryptic soy broth (TSB) for 1 h, 3h and 24h, and the concentration of leached Cu cation was determined with ICP-MS (Table S1). From Table S1, $Cu(OH)_2$ released higher levels of Cu^{2+} in TSB solution, as compared to CuO and Cu. The determined Cu^{2+} concentrations released from $Cu(OH)_2$, CuO and Cu surfaces were: 165 ppm, 45 ppm, and 9 ppm respectively, an expected observation as $Cu(OH)_2$ has greater surface area and greater solubility. In order to further probe the exact killing mechanism of these nanostructured surfaces, control experiments where *E.coli* was cultured with TSB spiked with 165 ppm of Cu^{2+} were performed. From Figure S1, TSB spiked with

165 ppm Cu^{2+} exhibited clear inhibition of *E. coli* growth in the first hour. This suggests that for the nanostructured surfaces, both contact killing and the release of Cu^{2+} play important role. The morphology of *E. coli* cells cultured on the different surfaces for 1 hour was characterized by SEM, as shown in Figure S2. It was hard to locate an intact *E. coli* cell on nanostructured surfaces as compared to smooth copper surfaces. This indicates an obvious killing effect by the structure.

These observations suggest that the good antimicrobial property of the nanostructured copper surface could be due to the synergistic effect of surface contact and the release of copper ions. The contact between the microbe cells with the nanostructured surface could lead to certain damage to the cell wall, and the subsequent entry of copper ions from the damaged cell wall further enhanced the killing performance.

We have established that Cu surfaces are able to eliminate including Gram negative bacteria, Gram positive bacteria and yeasts over a 24 hour period. From Figure 2, it was clear that nanostructured surfaces were able to eliminate microbial colonies much faster than plain copper surfaces. To elucidate the rate of microbe clearance, *E. coli* was selected as a representative for surface efficacy tests at shorter timepoints of 5 min, 15 min, and 30 min. As summarized in Figure S3a, the population of *E. coli* on nanostructured surface was fully eliminated, as compared to plain copper surface, which retained a concentration of microbes similar to the original concentration introduced on the surfaces. At the shorter timepoint of 5 min, viable *E. coli* was detected on all three surfaces, indicating that full killing of *E. coli* on the nanostructured surfaces happened between 5-15 min. Although full killing was not achieved in 5 minutes, a 2.6 and 3.3 log reduction of *E. coli* was observed for $Cu(OH)_2$ and CuO, respectively, which showed much faster antibacterial killing properties than plain copper at 5 min. Additionally, exposure of the microbe at even shorter timepoint of 1 min resulted in a 1.2 and 2.6 log reduction for $Cu(OH)_2$ and CuO, respectively (Figure S3b).

Hospital acquired infections and the emergence of antibiotic resistant strains are major threats to human health.[37-38] Other than the representative microbes described earlier, the excellent efficacy of the nanostructured surfaces was demonstrated against clinically isolated pathogens commonly found in a hospital setting.[39] These microbes include methicillin-resistant *S. aureus* (MRSA), carbapenem-resistant Gram negatives, vancomycin-resistant enterococci (VRE) and fungi (drug resistant *Candida* sp. e.g. *C. auris*). As shown in Table 1, both the $Cu(OH)_2$ nano-sword and CuO nano-foam surface eliminated all the test microbes, with no colonies found on the surface after a 24 h incubation.

Due to the overuse and misuse of antibiotics, antimicrobial resistant microbes have now become one of the most critical challenges in our society. Among these resistant microbes are a group called the ESKAPE pathogens (*E. faecium, S. aureus, K. pneumoniae, A. baumanii, P. aeruginosa* and *Enterobacter* sp.). To investigate if the fast killing property of the nanostructured surfaces was effective on ESKAPE pathogens as it was on *E.coli*, surface efficacy tests were performed with a short time point of 10 mins, where aliquots of the 6 pathogens were introduced onto the $Cu(OH)_2$ nano-sword surface. A 10 minute timepoint was selected, considering the complete elimination of *E. coli* happened between 5-15 min (Figure S3a), and the results summarized in Table 2.

Table 1. Antimicrobial efficacy of $Cu(OH)_2$ nano-sword and CuO nano-foam against clinically isolated pathogens

	$Cu(OH)_2$ nano-sword	**CuO nano-foam**
Microbe tested	**Log reduction**	
Staphylococcus aureus MRSA-RI0309N	10.0*	10.0*
Pseudomonas aeruginosa-CI0183A2	10.0*	10.0*
Acinetobacter baumannii-RI0139A	10.8*	10.8*
Vancomycin resistant *Enterococcus faecium - RI0252N1*)	11.9*	11.9*
Burkholderia cepacia – ATCC 700070	9.3*	9.3*
Escherichia coli –RI0157A	9.9*	9.9*
Serratia marcescens -CI0183A1	12.4*	12.4*
Klebsiella pneumoniae -CI0027	11.9*	11.9*
Klebsiella (Enterobacter) aerogenes, ESBL-positive, RI0006A2	9.6*	9.6*
Candida tropicalis-RI-0243A	6.6*	6.6*
Candida parapsilosis (ATCC 22019)	8.2*	8.2*
Candida auris (NCPF 8977)	10.1*	10.1*

* complete elimination of microbe after 24 h incubation.

Table 2. Antimicrobial efficacy of $Cu(OH)_2$ nano-sword against ESKAPE pathogens at 10 minute timepoint

	Cu foil	**$Cu(OH)_2$ nano-sword**
Microbe tested	**Log Reduction**	
***E**nterococcus faecium RI0252N1*	0.3	2.0 (5.4[#])
***S**taphylococcus aureus RI0309N*	0.0	5.4*
***K**lebsiella pneumoniae CI0027*	0.1	5.6*
***A**cinetobacter baumannii RI0139A*	0.0	4.9*
***P**seudomonas aeruginosa CI0183A2*	0.1	5.8*
*Klebsiella (**E**nterobacter) aerogenes RI0006A2*	0.2	6.0*

[#] For *E. faecium* partial killing at 10 min and a full killing was observed at 15 min.
* indicating complete elimination of microbe population with no viable colonies.

While multidrug-resistant bacteria and fungi pose a continual threat to human and public health, the current COVID-19 pandemic serves as a reminder that viruses are a present and constant threat. While antiviral efficacies are ideally determined using live, active viruses of interest, the challenges of using such virulent pathogens for experiments includes the requirement higher biosafety clearance for the labs. As such, many have reported the use of bacteriophages as viral surrogates, as they are structurally similar to many human and animal viruses, and are non-pathogenic towards humans.[40] P22 and MS2 were selected as viral surrogates for our study of the efficacy of our nanostructured materials against non-enveloped viruses.[41-42]

The efficacy of the surface was first determined with P22 and it was observed the population of the bacteriophage was eliminated at longer timepoints of 3 and 24 hours. At a shorter timepoint of 1 h, the surface bearing $Cu(OH)_2$ nano-swords was most the effective, with a 6.6 log reduction of the original titer, as compared to both bare Cu foil and CuO surfaces which effected about 1 log reduction (Figure S4). For MS2, a full elimination of the phage titer was achieved for $Cu(OH)_2$ surfaces in 15 min, as compared to 1.5 log reductions for Cu foil and 1.7 log reductions for CuO (Figure 3a). With these results in mind, these materials were evaluated for its surface antiviral efficacy against Murine Hepatitis Virus (MHV), an internationally accepted surrogate for SARS-CoV-2. A 2.4 log reduction was achieved for $Cu(OH)_2$ surfaces in 15 min, as compared to 0.9 log reductions for Cu foil and 1.6 log reduction for CuO (Figure 3b).

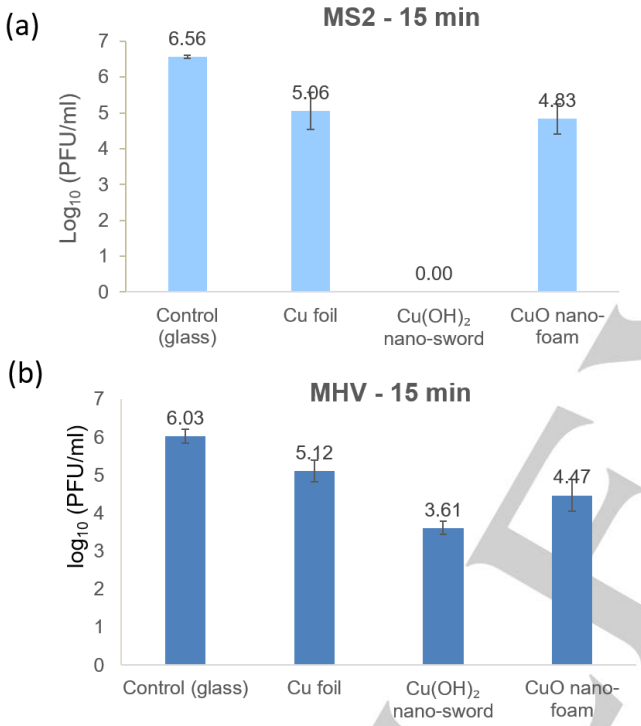

Figure 3. Antivirus properties of copper foil, $Cu(OH)_2$ nano-sword array surface, and CuO nano-foam surface against (a) MS2 bacteriophage and (b) Murine hepatitis virus at 15 min. Data are representative of three independent experiments and values are expressed in mean ± SD.

Bacteriophages such as P22, MS2, and enveloped viruses (exemplified by MHV) possess different structures as compared to bacteria and are of a much smaller size, with a typical diameter of less than 100 nm. Nano-patterned surfaces kill bacteria by physical rupture of the cell wall/membrane, however, to a much smaller virus (especially non-enveloped virus), this killing mechanism plays no role.[22, 43] It is well established that viruses are susceptible to the damage induced by copper via several potential mechanisms, including the damage of the encoding genes that are essential for viral infectivity and inducing the generation of reactive oxygen species (ROS) which acts on the viral envelope or capsid.[44-45] The fast killing property of our $Cu(OH)_2$ nano-sword material against bacteria is related to the fast Cu ion releasing capability (165 ppm in 1 hour) due to its greater surface area and greater solubility. However, 165 ppm of Cu(II) did not effect a significant reduction of the MS2 starting titer, as shown in Figure S5. Cu(I) has been reported to be more potent against viruses,[26] and this could be another factor that drives the increased potency of $Cu(OH)_2$ nano-sword against viruses. Compared to the over oxidized CuO blade surface, the $Cu(OH)_2$ nano-sword was synthesized under much milder conditions. The $Cu(OH)_2$ nano-sword surface could release Cu(I) due to the accessibility to plain copper surface and the interface between Cu(0) and $Cu(OH)_2$.[46] XPS studies were performed to elucidate the identity of the copper species present on the 3 surfaces. As shown in Figure S6, the presence of oxidised Cu species were detected on both $Cu(OH)_2$ nano-sword surface and CuO nano-foam surfaces, with the $Cu(OH)_2$ nano-sword surface containing more Cu(I) component as compared to CuO nano-foam surface.[47]

We have established that the nanostructured surfaces performed much better than plain copper, as antimicrobial surfaces. This will prove to be very useful for the disinfection of frequently touched surfaces. However, pathogens may be transmitted through other pathways such as through aerosol transmission. This is particularly prevalent for airborne viruses.[5-6, 48] Therein, we demonstrate the utility of nanostructured Cu surfaces as filters for air purification as shown in Figure 4.

The antimicrobial air filter was fabricated from copper wool, exposed to the conditions described earlier for the synthesis of $Cu(OH)_2$ nano-sword and CuO nano-foam, and the structures were subsequently confirmed by SEM (Figure S7). To demonstrate its functionality as an antimicrobial air filter, the $Cu/Cu(OH)_2$ wool was fitted into a transparent polycarbonate tube, with a fan fitted maintain a constant air flux of 0.0072 m^3/s, as shown in Figure 4. This device was subsequently placed in an enclosed room, with a total volume of 30.24 m^3. The calculated time for one cycle of air to pass though time was ~70 min. An air sampler was also used to monitor the bacterial concentration in the room. As shown in Figure 4, the microbe counts (aerobic bacterial colony counts) continually decreased to about 40% of its original number after 210 mins. Although a single pass through the filter should theoretically take about 70 mins, it should be noted that it is impossible for 100% of the microbes and air to pass through the filter due to the continuous motion of air and particles, thus explaining the slower rate of air disinfection as compared to the fast killing kinetics exhibited in Figures 2 and 3. A 40% microbial population decrease (of aerobic colony counts) after 210 minutes is significant nonetheless. For practical applications, these antimicrobial air filters can be fitted in the inlet of the ventilation system in an office/building for air disinfection, and may be offer an advantage as it does not involve any chemical disinfectants. We have also noticed that in dry air, the antimicrobial performance of the nanostructured filter was less significant as compared to the non-nanostructured filter. No copper ions will be released in dry air, leading to a weaker antimicrobial property.

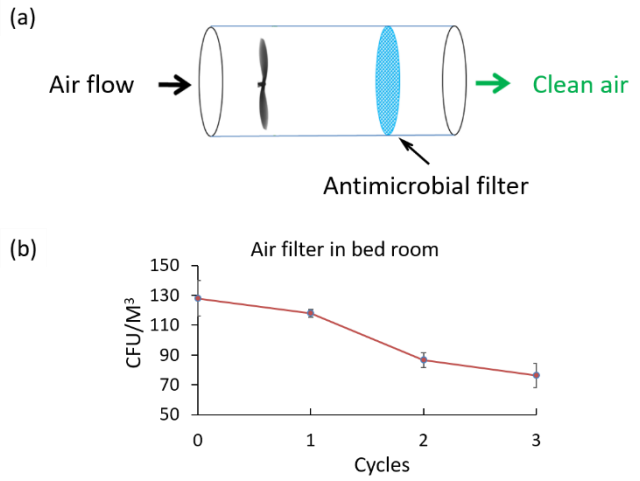

Figure 4. Antimicrobial air filter device by fitting a Cu/Cu(OH)$_2$ wool in the tube. (b) Air disinfection results by placing this device in an enclosed bedroom, and aerobic bacterial colony counts were monitored by plate counting technique by an air sampler.

Aside from touch surfaces and airborne transmission, contaminated water is another source of pathogen spread, especially for bacteria such as *E. coli*. To test the disinfection efficacy of our copper nanostructures in water, small chips of Cu/Cu(OH)$_2$ and Cu/CuO was used for the testing, with untreated Cu chips as positive control. The small chips was cut from the wool samples in Figure S7, where each chip was cut to size of 1 mm × 1 mm. 0.1 g of each sample was put to 10 ml of microbe solution, and left to incubate at room temperature. Viability of the microbe in solution was assessed by standard plate counts. As shown in Figure S8, Cu/Cu(OH)$_2$ and Cu/CuO were able to kill *E. coli*, *S. aureus* and *C. albicans* much faster than pristine Cu(0), within 1 hour. While promising, it should noted that the release of the copper ions into the environment may pose long term toxicology concerns.

In summary, Cu(OH)$_2$ nano-sword and CuO nano-foam arrays were successfully grown on copper surfaces by a simple chemical reaction. As compared to pristine copper surfaces, the nanostructured copper surfaces were able to eliminate microbes at a fast and efficient rate, due to synergistic killing mechanisms. These nanostructured copper surfaces have demonstrated their potential in breaking pathogen transmission pathways on surface, and in air and aqueous medium, with much better performances than the parent copper surfaces. Such nanostructured copper surfaces present promise for applications in hospitals, ICU wards, and other public areas, especially during our current pandemic situation.

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Keywords: antimicrobial materials • Cu(OH)$_2$ nanostructure • CuO nanostructure • air disinfection • water disinfection

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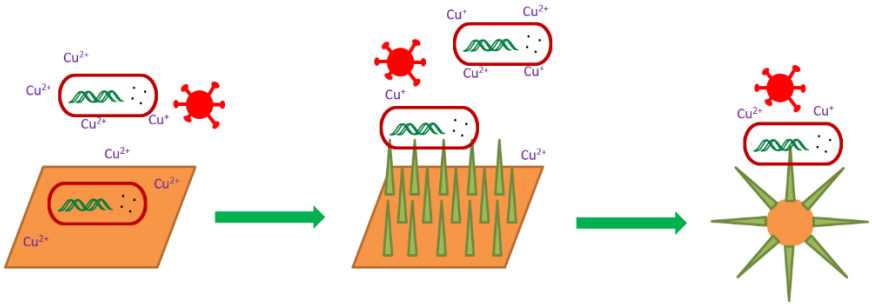

$Cu(OH)_2$ nano-sword and CuO nano-foam on copper were prepared and demonstrated superior antimicrobial property by eliminating ESKAPE pathogens and virus in minutes. Such materials present potential applicability in high traffic and healthcare functions, to end pathogen transmission pathways.