Water-Mediated *In Situ* Fabrication of CuI Nanoparticles on Flexible Cotton Fabrics as a Sustainable and Skin-Compatible Coating with Broad-Spectrum Antimicrobial Efficacy

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KEYWORDS

Copper Iodide, Nanoparticle, Coating, Antimicrobial, Sustainable, Skin-Compatible

ABSTRACT

Infectious pathogens, such as SARS-CoV-2, can remain viable on common fabric surfaces for days, posing a significant risk of fomite transmission. Antimicrobial coating is a widely employed approach for pathogen eradication upon direct contact. However, fabricating such coatings on fabric substrate mostly necessitates toxic organic solvents and complex equipment/processes. Most coatings also require a long contact time for complete disinfection, which may compromise their usefulness in mitigating the spread of highly infectious pathogens. Herein, we report a sustainable and scalable water-mediated method to prepare copper iodide (CuI) coating on flexible cotton fabrics, attaining highly potent antimicrobial efficacy and rapid germicidal kinetics. Only water is required as the processing solvent for the *in situ* formation of CuI nanoparticles on the substrate, and the unconsumed reagents can be fully recycled, making the reported method a green, economical, and zero-waste technology promising for industrial scale-up. Within just 2 minutes of contact, the coated cotton fabric containing 5.1wt.% CuI nanoparticles exhibits near complete inactivation of murine hepatitis coronavirus (>99.9%) and *Salmonella* bacteriophage P22 (>99.9999%) as models for the enveloped and non-enveloped viral species, respectively. It is also able to eliminate a variety of bacteria and fungi with 3.5 – 7.4 log reductions in 2 – 5 minutes. Further, in view of the robust durability and skin compatibility of the coating, this simple yet

powerful approach holds great promise for practical applications, especially in future infectious disease outbreaks.

1. INTRODUCTION

Fabrics are widely used in household, commercial, and healthcare facilities but lack intrinsic antimicrobial capability. Laboratory study found that viruses, including SARS-CoV-2 that caused the recent Covid-19 pandemic, can maintain their infectivity on common fabric for two days,[1-2] leading to severe transmission risks via the contaminated fabrics, or fomites.[3-6] Such indirect fomite transmission is one of the major ways of infection spread for many other pathogens, including multidrug-resistant bacteria and fungi. Treatment of fabrics with biocidal agents represents a promising strategy to decrease pathogen contamination and reduce the spread of infectious diseases. To this end, self-disinfecting coatings are becoming an increasingly popular practice to help contain the disease, especially at the early stages of an endemic/pandemic when other therapeutic options, such as vaccines and drugs, are yet in place.[7-8]

By virtue of its strong biocidal activity, low toxicity, and high abundance, copper has garnered immense interest as an antimicrobial coating agent for decades.[9-13] Between 2008 and 2011, the US Environmental Protection Agency (EPA) registered over 300 copper alloys as antimicrobials,[14] and their effectiveness against coronavirus was also recommended in 2021, emphasizing the great potential of copper-containing materials in the manufacturing of self-disinfecting surfaces. Copper nanoparticles (Cu NPs)-coated or -impregnated fabrics and textiles have also been explored for potential applications to prevent infection transmission.[15-20] Nonetheless, the colored metallic copper and Cu(II)-containing compounds usually require a long contact time of up to hours to eliminate the target, rendering them of limited value in mitigating the lateral transmission of highly

infectious pathogens.[10, 21-23] In contrast, many earlier studies have shown that the colorless copper(I) iodide (CuI) exhibits prominent antimicrobial activity and low toxicity that may serve as a more suitable coating precursor.[24-25] Most existing methods for CuI coating fabrication, unfortunately, require toxic acetonitrile as the processing solvent due to its poor solubility in other solvent systems.[16] Extensive use of acetonitrile may cause health problems to the workers and a severe impact on the environment. Some methods also require sophisticated instruments and special skills,[16, 26-28] further making them unsuitable for industrial manufacture and large-scale application (see Table S1 in the Supporting Information). Therefore, a simple and sustainable approach to preparing antimicrobial CuI coating on flexible fabrics is highly favorable but remains an unmet challenge.

We herein, for the first time, report a sustainable and scalable water-mediated method to fabricate highly potent antimicrobial CuI coating on flexible cotton fabrics.[29] Using water as the sole processing solvent, CuI nanoparticles can be *in situ* generated on the fabric surface, creating a colorless and durable coating with excellent antimicrobial efficacy. The coating exhibits near complete inactivation of both enveloped murine hepatitis virus (MHV, as a surrogate of the SARS-CoV species) and non-enveloped bacteriophage virus P22 in just 2 minutes of contact. It also shows remarkable antibacterial and antifungal activity, achieving 3.5 to 7.4 log reductions in 2 – 5 minutes against various bacterial and fungal pathogens. In addition, the coating was experimentally demonstrated to be of low cytotoxicity to fibroblast cells and highly compatible with the mouse skin, advancing it to a promising self-disinfecting technology for coating on general textiles, such as curtains, carpets, and bed sheets in public places like hospitals and hotels.

2. RESULTS AND DISCUSSION

2.1. Water-Mediated CuI Coating Design and Fabrication

The air-stable CuI, in the form of particles or thin films, has drawn extensive interest across different technological fields,[16, 24-25, 30] but the poor solubility of CuI in most solvents hinders its processability for practical use. In an aqueous solution containing excess KI (i.e., 3.5 M), the otherwise insoluble CuI can be readily dissolved by forming the linear $[I\text{-}Cu\text{-}I]^-$ anions.[31] More interestingly, simple dilution with water can re-generate the CuI as nanoparticles via *in situ* precipitation. Relying on this unusual property, we developed a simple and sustainable method to fabricate CuI coating on flexible cotton fabrics (Figure 1a) that features excellent antimicrobial activity, robust durability, and good skin compatibility. The aqueous solutions of NaI and NaCl at 3.5 M concentration were also examined, wherein the CuI solubility is much lower than that in the KI counterpart.

Cotton fabric was selected as the coating substrate because of its multifaceted favorable features including low cost, negative carbon footprint, physical tunability, and chemical modifiability. Thus, any straightforward modification on cotton could be integrated into the existing industrial infrastructures with ease.[32-34] As we believe a method would be more compatible with existing infrastructure if it can be demonstrated on the end product fabric, a 100% cotton shirt potentially with some dyeing/finishing treatment was purchased from a local store, cut into small swatches of 2 cm by 2 cm in size, and used as the coating substrate. It is also worth noting that our approach does not require any special chemistry on the cotton surface, hence, the dyeing and finishing chemicals on the cotton shirt would not affect the coating fabrication.

To prepare the coating, an aqueous solution containing CuI and excess KI was first drop-cast onto a cotton swatch and cured at 70 ^{o}C for 1 hour to ensure complete precursor impregnation. The swatch was then thoroughly rinsed for 6 times using 40 mL deionized water each time, a step that serves multiple purposes, including: (i) *in situ* on-surface precipitation of CuI nanoparticles, (ii)

removal of the loosely bound CuI particles, and (iii) dissolution of the unconsumed KI salt. Water was solely needed as the processing solvent, and both the excess CuI and unconsumed KI can be easily recycled for future use. There was no visual difference in the physical appearance of the CuI-coated cotton as compared to the pristine (insets to Figure 2a and 2b). No visible changes were observed either after storing the coated cotton in the air for over a year, evidencing its excellent stability at ambient conditions. In comparison to the coatings prepared using pre-formed particles, the CuI nanoparticles in this study were fabricated by on-site *in situ* precipitation directly on the cotton fabric, which would provide stronger anchoring to the substrate and more homogeneous coating agent distribution across the entire cotton fabric. In addition to the coordination bonding between Cu centers and the hydroxyl groups on cotton, retention of the particles could be further enhanced by physical anchoring and embedding of the *in situ* generated CuI nanoparticles on the substrate microfibers. Furthermore, to mitigate the potential impact on the environment, the CuI content loaded on cotton fabrics as coating agent can be recycled after dedicated use simply by rinsing with concentrated KI solution in water, wherein CuI can be readily dissolved in the solution and retrieved as precipitate with subsequent water dilution.

Such a simple '*drop-rinse-dry*' method, upon slight modification, is readily extendable to other flexible fabrics, such the hydrophobic polypropylene (Figure S1 in the Supporting Information). CuI nanoparticles can be i*n situ* generated on the polypropylene microfiber, and the fabric retained its hydrophobicity after coating. Demonstrated on both hydrophilic cotton and hydrophobic polypropylene, we believe this new coating method would be widely applicable to other flexible fabric and textile substrates for common use, which will be subjected to further investigations.

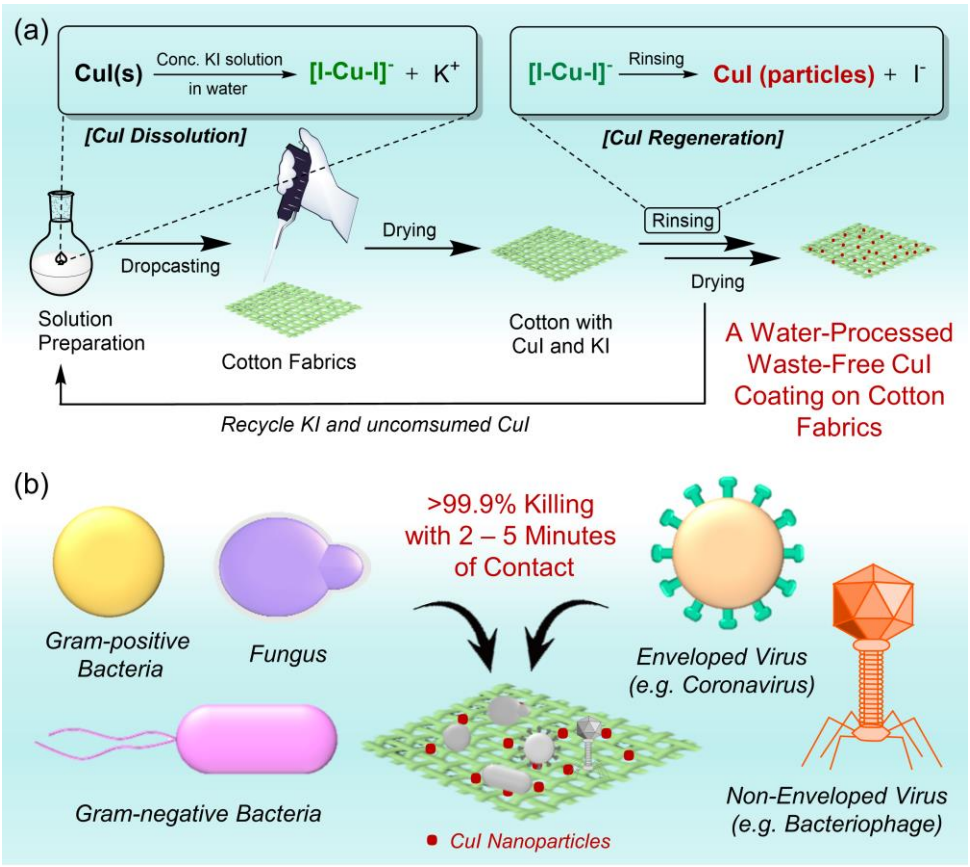

Figure. 1. (a) Schematic illustration of the CuI coating procedures on flexible cotton fabrics. (b) Conceptual scheme showing the rapid killing of various microbes and viruses by the water-mediated CuI coating. The drawings are not to scale.

2.2. Characterization of the CuI Coating

Field emission scanning electron microscope (FESEM) images of the cotton swatch were taken at different fabrication steps. After drop-casting the precursor solution, the substrate microfibers retained their original morphology and smooth surface (Figures 2a and S2), indicating that all precursors were embedded within the fiber. Following the rinse with excess water, granular particles with an average diameter of 885 nm were formed on the fiber surface (Figure 2b and 2c), which contain Cu and I elements with an atomic ratio of about 1:1 (Figures 2d-2f and S3). We note that such integration of functional coating agents at the fiber level is essential to maintain the

intrinsic feature of the substrate fabrics.[32] Alongside the particles on surface, Cu and I elements were also detected at the bare regions of the cotton microfiber (Figure 2e and 2f), implying the simple *'drop-rinse-dry'* method not only facilitates *in situ* formation of nanoparticles on the surface but also allows the precursors to disperse across the entire fabric substrate, which may contribute to the coating's high durability demonstrated in later sections.

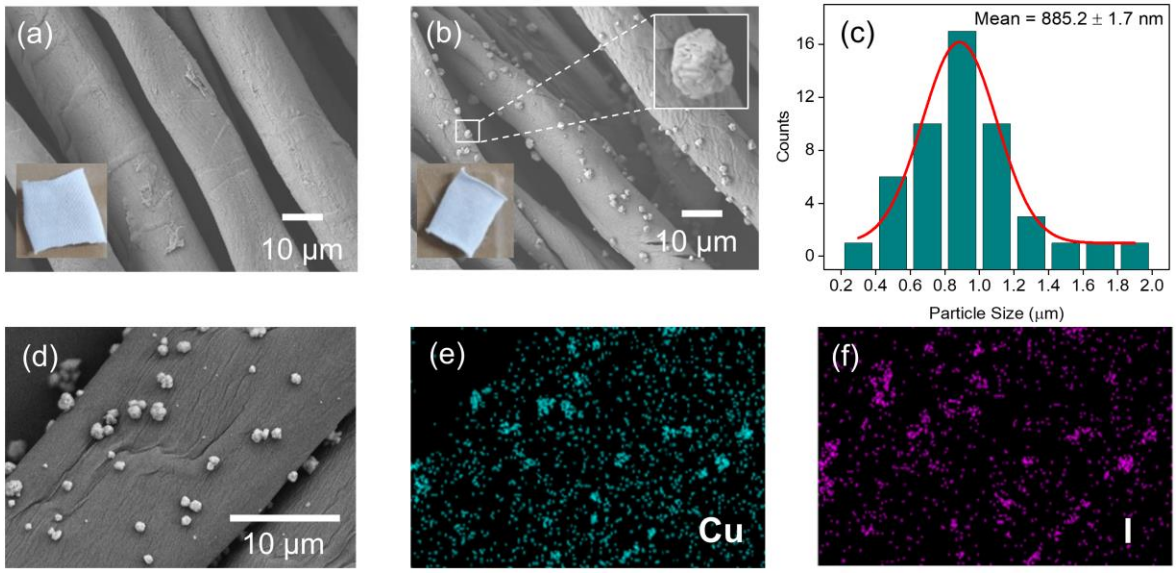

Figure. 2. Morphological characterization of the CuI-coated cotton fabrics: (a) pristine cotton microfibers; (b) CuI-coated cotton microfibers; digital pictures of the cotton swatches are also shown as inset to panels (a) and (b); (c) size distribution of the *in situ* generated CuI particles, (d-f) FESEM-EDX elemental mapping of Cu and I on the coated cotton surface.

Based on these observations, the most plausible coating formation mechanism could be as follows: drop-casting the solution impregnates the substrate with precursors in the form of K^+, $[I\text{-}Cu\text{-}I]^-$, and excess I^-; subsequent rinsing with water reduces the precursor concentration, leading to *in situ* re-generation of CuI nanoparticles both within and on the surface of the cotton microfiber. Some CuI particles would fall off from the fiber surface during the rinsing step, which can be recovered by centrifugation and quantified to be ~ 40% of the initial drop-cast amount. Moreover,

all the KI salt was rinsed away with water, verified by the absence of the K element on the CuI-coated cotton (Figure S3). The rinsed-away KI can be retrieved by evaporating the water and recycled for subsequent coating fabrications. In other words, zero waste was generated throughout the entire coating fabrication process, making our method a sustainable and economically viable option suitable for industrial scale-up.

In the powder X-ray diffraction (pXRD) patterns, the new peaks at 25.6°, 30.0°, 42.3°, 50.1° and 52.6° for the coated samples can be unambiguously assigned to the (111), (200), (220), (311) and (222) crystal planes of γ-CuI (Figure 3a).[35] All other peaks are from the cellulose microcrystalline domains in the substrate, which remain almost identical to that of pristine cotton, indicating the intact substrate crystallinity after coating.[34] X-ray photoelectron spectroscopy (XPS) analysis also shows the presence of Cu and I on the coated surface (Figure 3b). Specifically, from the high-resolution Cu *2p* scan, the spin-orbit splitting at 933 eV for Cu $2p_{3/2}$ and 953 eV for Cu $2p_{1/2}$, as well as the absence of satellite peaks at around 943 eV suggested that copper mostly existed as Cu^{+}, instead of Cu^{2+} or Cu^{0} (Figure 3c).[36-37] Deconvolution of the Cu *2p* peaks presents two different Cu^{+} environments in the CuI particles, which can be assigned to those on the surface and in bulk, respectively.[38] The +1 oxidation state of copper can also be substantiated by the Cu LMM peak at 572.3 eV (a distinct feature of Cu^{+}, Figure 3d).[39-40] The high-resolution I *3d* scan exhibited the characteristic well-separated spin-orbit components at around 632 eV for I $3d_{3/2}$ and 621 eV for I $3d_{5/2}$, concurring well with the presence of iodide anions (Figure 3e).[41] As expected, peak deconvolution gives two distinct environments for iodide, corresponding to those of on-surface and in-bulk origins respectively.

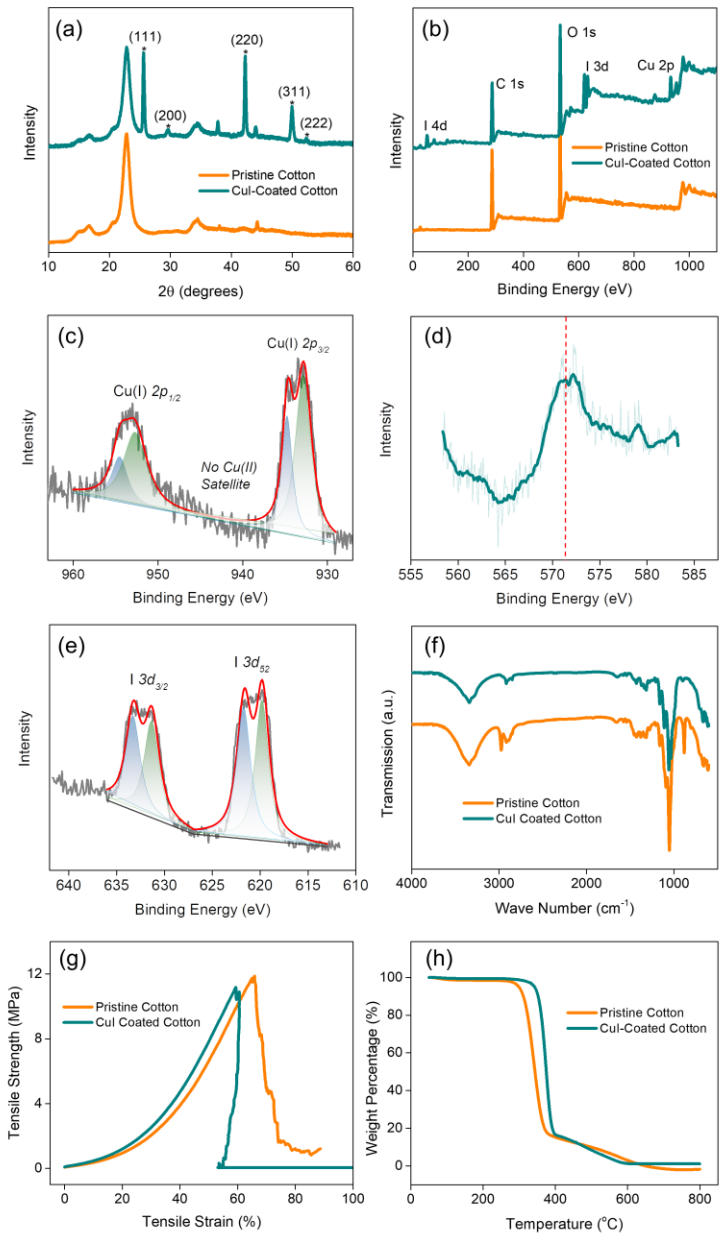

Figure. 3. Characterization of the pristine and CuI-coated cotton fabrics: (a) powder X-ray diffraction patterns showing new peaks of γ-CuI after coating; (b) X-ray photoelectron spectroscopy (XPS) survey scan; (c) high-resolution XPS scan of the Cu *2p* region confirming the +1 oxidation state of Cu; (d) XPS Cu LMM spectrum; (e) high-resolution XPS scan of the I *3d* region; (f) FTIR-Attenuated Total Reflectance (ATR) spectra; (g) tensile strength profiles; (h) thermal gravimetric analysis (TGA) results.

The Fourier transform infrared attenuated total reflectance (FTIR-ATR) spectrum of the CuI-coated cotton resembles that of the pristine (Figure 3f), confirming the chemical structure of the cotton substrate was not affected by the coating. The reduced intensity of some FTIR peaks can be ascribed to the coverage of the underlying cellulose by CuI. The mechanical property of the coated cotton was found comparable to that of the uncoated, both displaying tensile strength of about 12 MPa at strains of 60 – 70% (Figures 3g and S4). Interestingly, the CuI-coated cotton displayed enhanced thermal stability relative to the pristine, demonstrated experimentally by the thermal gravimetric analysis (TGA) results wherein the coated cotton was thermally stable up to around 350 ^{o}C in the air, while the pristine started to decompose at about 280 ^{o}C (Figure 3h). This could be due to the residual inorganic CuI within the cotton microfibers that improves the thermal stability of cellulose.[42] Taken together, all these comparative characterizations reveal the fact that the CuI coating does not compromise the intrinsic chemical and physical properties of the cotton substrate, but brings fascinating germicidal activities as detailed in the following discussions.

2.3. Antiviral Activity against the Enveloped Coronavirus

CuI has long been of central research interests for antiviral applications.[24, 43] A recent study by Takeda *et al.* clearly unveiled the capability of CuI to damage the genomes and proteins of SARS-CoV-2.[43] Therefore, we hypothesize the CuI-coated fabrics to exhibit potent anti-coronavirus efficacy, and we confirm it with the experiments as follows.

A BSL-2 SARS-CoV surrogate, namely murine hepatitis virus (MHV), was used for the antiviral evaluation, which is a mice-infecting enveloped positive-sense RNA coronavirus sharing high structural similarity with the SARS-CoV species.[44-46] The anti-MHV activity was determined using the plaque-counting assay (Figure S5). In brief, 100 μL of MHV (10^6 – 10^7 PFU mL^{-1}) was added as separate droplets onto the surface of the CuI-coated and pristine (as negative control)

cotton swatches. Like the pristine, the CuI-coated cotton remains highly hydrophilic, and the viral droplets can be immediately absorbed into the coated fabrics. Such fast wetting is important to facilitate intimate contact between the viral particles and the CuI coating, which is essential for the subsequent rapid killing action.[5] After specified contact times, the surviving MHV loads on the fabric were recovered and quantified using NCTC 1469 mouse liver cells as the host for plaque formation.

For coatings against highly infectious pathogens, rapid killing kinetics is perhaps the most important design target to halt the spread of infection. Thus, the CuI coating was first evaluated on its anti-MHV efficacy with various contact times ranging from 30 seconds to 15 minutes (Figure 4a). The plaque assay results showed that with contact times of 2 minutes or longer, no viable MHV could be recovered from the cotton swatch coated with 3.8 mg CuI (i.e., 0.95 mg per square centimeter of the cotton fabric, or 5.1% in weight percentage), indicating that the antiviral efficacy was beyond the limit of detection for the plaque assays used (i.e. 99.9%). As an additional note, the antiviral performance was also assessed at laboratory conditions with and without the light on, and no activity difference was observed, indicating the absence of photo-related effect for the CuI-coating. Even with contact times as short as 30 seconds and 1 minute, the average antiviral efficiency was still as high as 97.8% and 99.6% respectively, signifying the extremely fast virucidal kinetics by the water-mediated CuI coating.

Next, with a fixed contact time of 2 minutes, the amount of CuI drop-cast on each cotton swatch was varied, ranging from 0.38 mg to 6.0 mg. It is worth noting that the actual CuI amount on the coated samples is less than the amount drop-cast, because some CuI would fall off as loose particles during the water rinsing step. For instance, a cotton swatch drop-cast with 6.0 mg CuI was determined to have 3.8 mg remaining on the substrate after rinsing. As shown in Figure 4b,

coated cotton swatch with different CuI amounts drop-cast demonstrated MHV inactivation in a dose-dependent manner. For the sample with 0.38 mg CuI drop-cast, only 56.8% of the virus was eradicated after 2 minutes of contact. With the same contact period, the anti-MHV efficacy increased to 83.6%, 97.5%, 99.8% and >99.9% with 0.75 mg, 1.5 mg, 3.0 mg and 6.0 mg of CuI drop-cast, respectively.

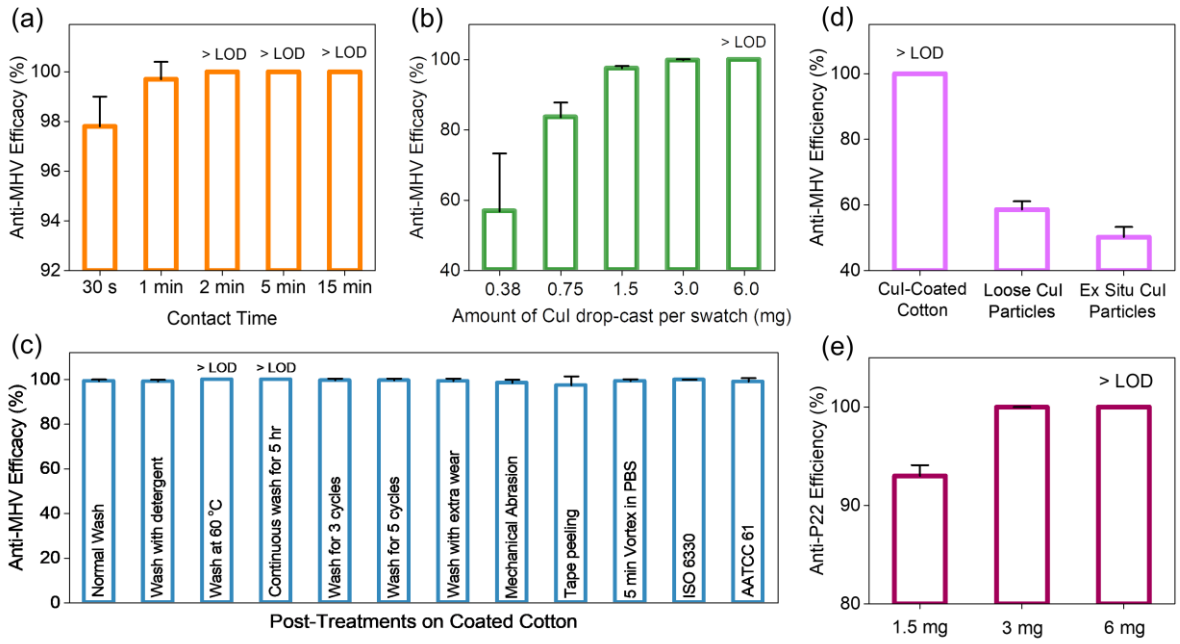

Figure. 4. (a-d) Antiviral efficacy against the enveloped murine hepatitis virus (MHV) as a surrogate for the SARS-CoV species: (a) effect of contact times for cotton swatches coated with 3.8 mg CuI; (b) effect of CuI amount drop-cast; (c) durability of cotton swatches coated with 3.8 mg CuI against various washing and mechanical post-treatment conditions; (d) results of control experiments using loose CuI particles or without addition of KI to dissolve the CuI (*ex situ* particles); the contact times for results shown in (b-d) were all fixed at 2 minutes; the limit of detection (LOD) of anti-MHV assay is 99.9%. (e) Antiviral efficacy of the CuI-coated cotton fabrics against the non-enveloped *Salmonella* bacteriophage P22 with different amount of CuI drop-cast; LOD of the anti-P22 assay is 99.9999%. Each test was repeated three times (n = 3), and the average value is reported with standard deviation as the error bar.

Aiming at practical use, durability of the cotton swatch coated with 3.8 mg CuI was challenged against a variety of washing and mechanical post-treatment conditions. To mimic a typical laundry process, the CuI-coated cotton swatches were immersed in water and stirred at 300 rpm for 1 hour. Several harsher conditions, such as washing with detergent (Dynamo Power Gel Laundry Detergent, 0.4%), high temperature (60 ºC), prolonged duration (5 hours), multiple washing cycles (×3, ×5, each equivalent to five domestic washing cycles), and the presence of other "*laundry*" (mimicked by five aluminum blocks of average mass ~100 mg), were investigated (see Table S2 in the Supporting Information for details). The effects of mechanical damage such as abrasion over sandpaper and tape peeling on the coating durability were also examined.[33] These post-treated samples retained most of their antiviral activities, showing 97.4% to >99.9% MHV inactivation rates after 2 minutes of contact (Figure 4c). To probe the loss of CuI particles after washing, we measured the light transmission of the washing solution at 600 nm, and no significant difference was observed between the pristine and coated samples. Quantitatively, a calibration curve for the relation between light transmission and the free CuI nanoparticle concentration in water was established, and the CuI loss was determined to be negligible (Figure S6). In a more extreme case, the coated sample was vortexed vigorously at the maximum speed using the GENIE2 vortex mixer for 5 minutes, and the coating still displayed a satisfactory antiviral efficacy of 99.3% with 2 minutes of contact, implying exceptional robustness of the water-mediated CuI coating. FESEM images of the coated cotton after post-treatments showed retention of the CuI nanoparticles on the cotton microfiber (Figure S7), which agrees well with the robust antiviral performances shown above. In addition, post-treatment experiments following the industry standards ISO 6330 and AATCC 61 were conducted, wherein the coating after treatment demonstrated 99.9% and 99.0% MHV inactivation rates respectively with a contact time of 2 minutes. The coating also maintained

its highly potent antiviral activity after being stored at ambient conditions for a year, displaying identical anti-MHV efficacy to the fresh sample, which indicates negligible effect of air oxidation on the virucidal property.

We wondered whether the antiviral result from the plaque assay was affected by the minimal amount of CuI particles fallen off during the test, which may continue inactivating the recovered viruses after the stipulated contact time, causing an overestimation of the antiviral efficacy. To this end, the antiviral effect of loose CuI particles was investigated, though we believe they should be minor in amount following the extensive water rinsing step during sample preparation. Since it was estimated that each CuI-coated cotton swatch was loaded with approximately 3.8 mg CuI, we considered the worst-case scenario wherein all CuI was leached out from the coated cotton into the solution. Therefore, 3.8 mg of free CuI particles, which were freshly regenerated by diluting a solution containing CuI and KI, were added to the media containing an uncoated cotton swatch inoculated with the MHV virus. Subsequent plaque assays revealed that the free CuI particles only induced a viral inactivation effect of 58.6% (Figure 4d). Due to the hydrophilicity of the coated cotton fabrics, viruses upon drop-casting on the sample can achieve intimate contact with the CuI particles, leading to the fast killing actions; however, if the CuI content is suspended in the media, the viruses would have little opportunity to get surface contact with the particle, giving rise to the compromised killing effect. Such contrasting results clearly confirm that the rapid viral inactivation indeed occurs during the stipulated contact time, and the presence of CuI in the incubation media (if any) should have no or only minor effect on the overall antiviral performance.

To demonstrate the importance of adding in KI to completely dissolve CuI for the *in situ* coating fabrication, we further evaluated the anti-MHV activity of *ex situ* coated cotton fabrics prepared by drop-casting a suspension of 3.8 mg CuI in 200 μL DI water (without KI added). With

identical contact time of 2 minutes, only 50.2% antiviral efficacy was achieved (Figure 4d). This inferiority could be attributable to the weak physical adsorption between the *ex situ* CuI particles and the cotton substrate, as compared to that prepared by the '*drop-rinse-dry*' *in situ* method. Thus, most of the *ex situ* particles will be rinsed off during sample preparation, leaving behind only a limited amount on the cotton fabrics.

2.4. Antiviral Activity against the Non-Enveloped *Salmonella* Bacteriophage P22

In contrast to the enveloped coronavirus protected by lipid membrane, non-enveloped viruses adopt simpler biological structures, mainly consisting of genetic materials encapsulated in a protein capsid. We employed *Salmonella* bacteriophage P22 as a model non-enveloped virus to further evaluate the antiviral performance of the water-mediated CuI coating. The testing was conducted in a similar manner to that for MHV (see the **EXPERIMENTAL SECTION** for details), except that the recovered P22 was quantified using soft agar plates inoculated with *Salmonella Typhimurium*. Results showed that the coated cotton swatch loaded with 3.8 mg CuI was able to inactivate over 99.9999% of the P22 (6 log reduction) within just 2 minutes of contact. By reducing the drop-cast CuI amount to 3.0 mg and 1.5 mg, the inactivation efficiency decreases to 99.99% and 93.0%, respectively (Figure 4e).

2.5. Antimicrobial Activities against Bacteria and Fungi

The antimicrobial performance of the CuI coating was evaluated against four bacterial strains, including Gram-negative *Escherichia coli (E. coli), Pseudomonas aeruginosa (P. aeruginosa), Acinetobacter baumannii (A. baumannii),* and Gram-positive *Staphylococcus aureus (S. aureus),* as well as a fungal species *Candida albicans (C. albicans)*. These microbes were selected as representatives of the common opportunistic human pathogens, causing severe infections and

healthcare burdens in the population. In brief, overnight-cultured microbial suspension was directly dropped as separate droplets onto the sample surface; after specified contact times, the surviving microbial cells were recovered and quantified using standard agar plating technique.

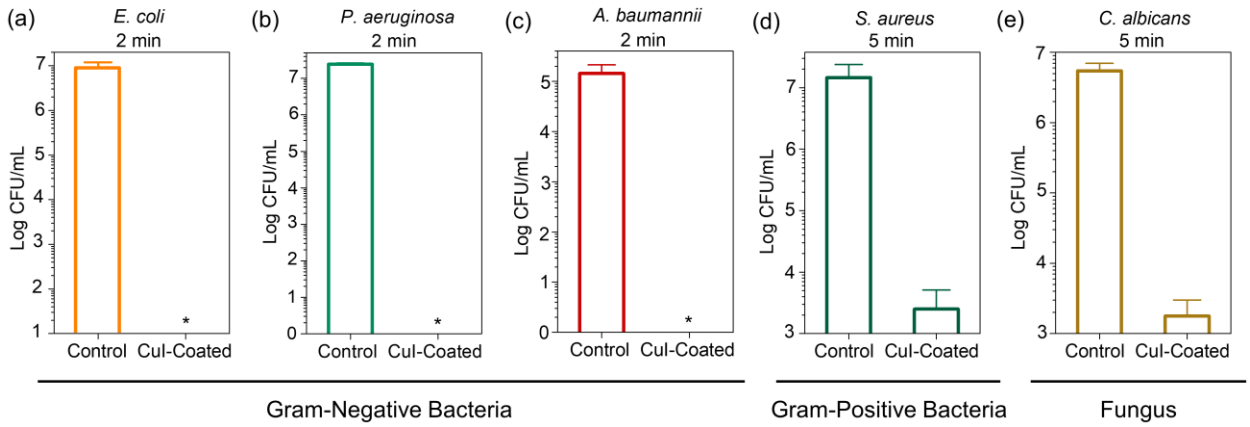

Figure. 5. CuI-coated cotton fabrics rapidly kill a broad spectrum of bacterial and fungal species, including (a) *E. coli*, (b) *P. aeruginosa*, (c) *A. baumannii*, (d) *S. aureus,* and (e) *C. albicans*. The contact times needed to achieve shown inactivation rates are also indicated. Each test was repeated three times (n = 3), and the average is reported with standard deviation as the error bar. Asterisk indicates that no colonies were observed.

Mirroring the excellent antiviral performance, the CuI coating also displayed highly potent antibacterial and antifungal efficacy against all the strains tested within 2 – 5 minutes of contact (Figure 5). In particular, the coating was found to be more effective against the Gram-negative strains (i.e., *E. coli*, *P. aeruginosa*, and *A. baumannii*) showing 5.2 – 7.4 log reductions after just 2 minutes of contact, as compared to the Gram-positive *S. aureus* and fungus *C. albicans* with 3.8 and 3.5 log reductions, respectively, in 5 minutes. Such strain specific bactericidal activity could be ascribed to the thinner cell walls of Gram-negative bacteria, as compared to the Gram-positive.[25] In contrast, free CuI particles were also examined and no parallel microbial killing effect was observed, confirming that the rapid killing occurs during the stipulated contact times, instead of

any other steps during the test. The morphology of *E. coli* (as a representative of the microbial species tested) cells was observed using FESEM. As shown in Figure S8, the bacterial cells maintained their original ellipsoidal shape and intact cell membrane on pristine cotton, while '*damaged*' and '*deflated*' cells were present on the CuI-coated fabrics, which aligns well with the strong bactericidal effect of the coating.

Though according to Centers for Disease Control and Prevention (CDC) the SARS-CoV-2 transmission via fabric or other porous surfaces is a rare possibility, the coating's highly potent and broad-spectrum germicidal effect against other non-enveloped viruses, bacteria, and fungi still render it a particularly useful technology to prevent infectious disease spread in various settings, especially hospitals, clinics, and nursing homes to battle against healthcare associated infections (HAIs).

2.6. Antimicrobial Mechanism

It is well known that copper-containing materials inactivate infectious pathogens mainly via three different mechanisms, namely release of copper cations, reaction oxygen species (ROS) generation, and direct surface contact.[47-49] To disentangle these factors, we incubated a suspension of CuI particles in respective growth media for 2 minutes and retrieved the clear supernatant by centrifugation. If there are any Cu cations released, they will be in the supernatant. Experimental results showed that mixing such supernatant with the pathogens did not induce any killing effect, implying that release of copper cations is not the major mechanism of antimicrobial action for the CuI-coated cotton fabrics. Despite ROS generation was reported before to account for the antimicrobial property of CuI and some other materials,[24, 50-53] we speculate that it is not the main mechanism for the CuI-coated cotton fabrics, because: (i) the presence of ROS in the CuI suspension was not detected with multiple attempts using 1,3-Diphenylisobenzofuran (DPBF) as

the probe,[54] (ii) the CuI-coated fabrics need much shorter contact time to inactivate pathogens, as compared to that in previous examples,[24, 43] and (iii) the pathogen inactivation effect can be generally observed for both metabolically active (e.g. bacteria, fungi) and inactive pathogens (e.g. viruses), and also persists in the dark. Therefore, direct surface contact is believed to be the major antimicrobial mechanism of the CuI-coated cotton fabrics, aligning with previous studies on other antiviral Cu(I)-based compounds.[55]

2.7. *In Vitro* Cytotoxicity and Skin Compatibility

According to the safety standards for antimicrobial textiles, evaluation of cytotoxicity and skin compatibility should be carried out in pre-clinical models.[56] The *in vitro* cytotoxicity of the water-mediated CuI coating was thereby assessed on L929 mouse fibroblast cells using the alamar blue cell viability assay. It is believed that cytotoxicity of the coating will be mainly induced by the CuI particles falling off from the coating (if any). Therefore, we incubated the CuI-coated cotton swatch with cell growth media to obtain the extract, and then used it to replace the spent media of L929 cell monolayer and followed by incubation for another 24 hours at 37 ºC. Results showed a cell viability rate of 93.6 ± 8.4%, signifying no apparent cytotoxicity from the CuI coating. This is also in good agreement with the fact that majority of the CuI nanoparticles were retained on the cotton fabric after post-treatment in water.

Skin compatibility of the coating was evaluated using a mouse model. As shown in Figure 6a, the back hairs of mice were shaved before securing a pristine and a CuI-coated cotton to the skin exposed. After four days, neither erythema nor edema were observed on the skins, and all the hairs grew back as normal. Haematoxylin and eosin (H&E) staining of the paraffin-embedded skin tissue which was in contact with the fabrics did not reveal any obvious histopathological abnormalities (Figure 6b and 6c). These results echo the previous finding wherein CuI

nanoparticles displayed excellent safety profiles through a variety of tests, including acute oral toxicity (LD_{50} > 2000 mg Kg^{-1}), eye irritation, primary skin irritation, skin sensitization, and mutagenicity.[43]

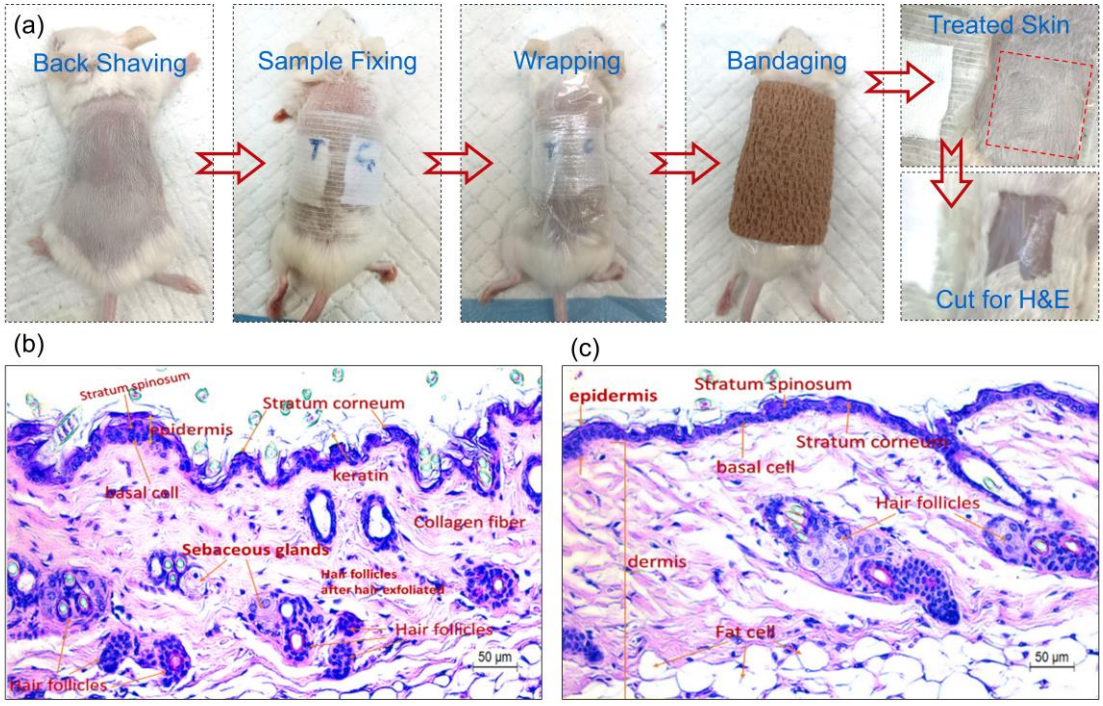

Figure. 6. Skin compatibility of the CuI-coated cotton swatches using a mouse model: (a) digital photographs showing a mouse at different steps of the test; typical H&E staining images of the skin tissue in contact with (b) pristine and (c) CuI-coated cotton for four days. Similar physical appearance and H&E skin tissue images were observed for all other mice in the group (n = 5).

3. CONCLUSION

A water-mediated sustainable and scalable approach to fabricate CuI coating on cotton fabrics was demonstrated, which renders the flexible substrate with broad-spectrum antimicrobial efficacy and rapid killing kinetics. The fabrication only involves facile '*drop-rinse-dry*' steps with water as the sole processing solvent, but readily produces a durable coating comprising *in situ* generated CuI

nanoparticles on the substrate surface. The colorless coating maintained the original appearance and physiochemical properties of the cotton substrate, while imparted excellent germicidal activities. Within just 2 minutes of contact, the coated cotton fabrics containing 5.1wt.% CuI nanoparticles can achieve near complete (>99.9%) inactivation of a wide range of viral, bacterial, and fungal species. More remarkably, the coating was experimentally demonstrated to be non-toxic to fibroblast cells at *in vitro* conditions and non-irritating to the mouse skin. In a time when the spread of highly infectious pathogens like SARS-CoV-2 is greatly impacting lives and economies, a simple yet highly potent self-disinfecting coating that displays rapid-killing germicidal performance would help reinforce the global efforts in fighting against the pandemics.

4. EXPERIMENTAL SECTION

4.1. Chemicals and Materials: Copper iodide (CuI) and potassium iodide (KI) were purchased from Sigma-Aldrich. Dichloromethane obtained from Honeywell and ethanol obtained from Fisher Scientific were used for substrate washing purposes. The cotton substrates were obtained by cutting a 100% cotton shirt (purchased from a local supplier) into 2 cm × 2 cm swatches. All chemicals were used as received unless otherwise specified. Mouse liver cells (NCTC 1469) were purchased from CLS Cell Lines service GmbH. *Escherichia coli* (*E. coli*, ATCC 25922), *Pseudomonas aeruginosa* (*P. aeruginosa,* ATCC 9027), *Acinetobacter baumannii* (*A. baumannii,* ATCC 19606), *Staphylococcus aureus* (*S. aureus*, ATCC 6538), and *Candida albicans* (*C. albicans,* ATCC 10231) were obtained from ATCC and reconstituted based on the recommended protocols. Mouse hepatitis virus (MHV-A59) was a kind donation from Yee Joo Tan (Institute of Molecular and Cell Biology, Singapore). Mueller Hinton broth (MHB) was purchased from BD Diagnostics (Singapore) and was prepared according to the manufacturer's instructions.

4.2. Coating Fabrication: The coating was fabricated using an easy-to-control '*drop-rinse-dry*' method. In brief, 7.3 g of potassium iodide (KI) was first dissolved in 12.5 mL of deionized (DI) water. 380 mg of CuI was then added to the KI solution and the mixture was stirred at room temperature until fully dissolved. 100 μL of the pale-yellow solution was drop-cast onto the cotton swatch successively, for a total of two times with 5 minutes interval. The drop-cast cotton was then dried in a preheated oven at 70 ^{o}C for 1 hour, and then rinsed with DI water for six times in total (40 mL each time). The cotton samples were then dried in a preheated oven at 70 ^{o}C overnight and stored at ambient condition until further analysis.

4.3. Coating Characterization: The FESEM images and EDX spectra were recorded using JEOL JSM-7400F (Japan). Pt coating was applied using JEOL JFC-1600 high-resolution sputter coater to improve the conductivity. Powder XRD was performed using Bruker D8 Discover GADDS 1.5418 Å (40 kV, 40 mA). The XPS data was obtained using Thermo Scientific Theta Probe equipment with a monochromatized Al Kα X-ray source of 1486.71 eV photons, a pass energy of 200 eV for survey scan and 40 eV for high resolution scan, and a photoelectron take-off angle (α) of 50° with respect to surface normal. The FTIR-ATR spectra were obtained using a PerkinElmer Spectrum 100 FTIR spectrometer. TGA was performed using PerkinElmer Thermogravimetric Analyzer (Pyris1). The tensile strength was measured using Instron 5569 Table Universal testing machine using samples of 2 cm × 10 cm in size.

4.4. Antiviral Test against MHV: The anti-MHV performance was evaluated on the murine hepatitis virus (MHV) by plaque assays with mouse liver cells (NCTC 1469) as the host. To perform the assay, 1.0 – 1.2 million cells were seeded in each well of a six-well cell culture plate and incubated at 37 ^{o}C overnight in 5% CO_2 atmosphere. Pristine cotton swatch was used as negative control. Both the samples and controls were sterilized under UV for 15 minutes prior to

the test. 100 µL of MHV (~ 10^6 – 10^7 PFU mL^{-1}) was then added as separate droplets on each cotton swatch to ensure uniform distribution. After desired contact times, the respective samples were vortexed in 10 mL of DMEM for about 30 seconds to recover the remaining viruses. After the vortex, 1 mL aliquot was taken and serial diluted in DMEM containing 1% PenStrep and 2% horse serum. 500 µL of viral solution with desired dilution factors was incubated with the cells for 1 hour at 37 ºC with intermittent shaking to keep the cell layer moist. Afterwards, a warm mixture of DMEM and agarose (final conc. 0.8 w/v%) was added into each well and left to solidify before incubating at 37 ºC with 5% CO_2 for another two days. The cells were then fixed with 10% neutral buffered formalin and stained with 5% crystal violet solution to visualize the plaques. The viral titer was calculated by multiplying the average number of plaques per well by the serial dilution factors. The antiviral efficacy (%) = ([viral titer from control] – [viral titer from sample])/[viral titer from control] × 100%. In general, about 10% of the viral load can be recovered from the pristine cotton fabrics after 2 minutes. The experiments were performed in triplicates, and results were expressed as the mean antiviral efficacy ± standard deviation (mean ± SD).

4.5. Antiviral Test against P22: The anti-P22 activity was evaluated using similar plaque assay as described above with modification. Briefly, 50 µL of P22 (~ 10^8 PFU mL^{-1} in Mueller Hinton Broth) was added to each cotton piece. After the specified contact time, each cotton was placed into 5 mL PBS and vortexed for 5 × 5 seconds to detach the P22 bacteriophage. The cotton swatches were then removed immediately, and the solution was centrifuged at 3500 rpm for 5 minutes to remove any CuI particles that may have detached. The supernatant was then subject to 10-fold serial dilutions accordingly. For each sample, 250 µL of supernatant was added to a mixture of 5.5 mL of soft agar (prepared from 4.5 g American Bacteriological Agar and 7.5 g LB broth in 500 mL DI water) and 50 µL of the overnight-cultured *salmonella* suspension. After

vortex briefly, the mixture was poured into agar plates (made from LB agar powder, Miller), with four replicates per sample, and left to solidify for 20 minutes. For each control, a mixture of 5.5 mL of soft agar and 50 µL of overnight-cultured *salmonella* suspension was first poured into agar plates and left to solidify for 20 minutes. 5 µL of each control dilution was then dotted on the soft agar, with two replicates per control, and left to dry for 20 minutes. The sample and control plates were then incubated at 37 ºC overnight and the plaques were counted the next day. The results were expressed as the mean antiviral efficacy ± standard deviation (mean ± SD).

4.6. Antimicrobial Test against Bacteria and Fungus: Antimicrobial tests were conducted using five different strains of microbes, including Gram-negative *E. coli*, *P. aeruginosa*, *A. baumannii*, and Gram-positive *S. aureus*, as well as a fungal species *C. albicans*. 100 µL of overnight microbial culture in MHB was added at separate areas on each cotton swatch to ensure uniform distribution. After the desired contact times, the respective samples were placed into 5 mL PBS and vortexed for 5 minutes to detach the remaining microbes. The samples were then removed, and the liquid was subject to 10-fold serial dilutions accordingly, before quantification using standard agar plating techniques. The experiments were performed in triplicates, and results were expressed as the mean antimicrobial efficacy ± standard deviation (mean ± SD).

4.7. *In Vitro* Cytotoxicity Test: *In vitro* cytotoxicity of the CuI coating against L929 Mouse Fibroblast Cells was evaluated using the alamar blue (ThermoFisher, USA) assay. The coated cotton swatches (2 cm × 2 cm) were immersed in 5 mL DMEM, vortexed for 30 seconds, and incubated at room temperature for 30 minutes to obtain the sample extract. L929 cells were seeded into a 96-well plate with a density of ~ 5×10^3 cells per well, and incubated at 37 ºC, 5% CO_2 for 24 hours. The spent media was removed with care and replaced with 100 µL of the extract. The plates were incubated at 37 ºC, 5% CO_2 for another 24 hours. The spent extract was then removed,

replaced with fresh media containing alamar blue (10%, v/v), and incubated for 3 hours in the dark. Fluorescence was measured using microplate reader (Tecan, Switzerland) with 560 nm excitation and 590 nm emission. Cell layer without treatment was used as positive control, and alamar blue solution itself was used as negative control. The percentage of cell viability was defined as Viability (%) = [(F590 of the treated sample – F590 of the negative control)/(F590 of positive control – F590 of negative control)] × 100%. The experiments were performed in triplicates, and results were expressed as the mean antiviral efficacy ± standard deviation (mean ± SD).

4.8. Skin Compatibility Test: The skin compatibility experiment was conducted using five BALB/c mice (8 – 12 weeks old, 18 – 22 g body weight) per group. All experiments were conducted in accordance with the approved protocol #221697 from the Institutional Animal Care and Use Committee (IACUC) at the A*STAR Biological Resource Center of Singapore. In brief, the mice were anesthetized and their backs were shaved to expose an area of at least 3 cm × 5 cm of skin. On each mouse, one piece of CuI-coated cotton swatch (sample) and one piece of pristine cotton swatch (control) was secured to the skin of the mice with SurgiStrip reinforced skin closures. The backs of the mice were then covered with AsGUARD film dressing and the mice were bound with an elastic bandage to ensure that the cottons remained secured. The mice were free to move around for the next four days, before they were anaesthetized and sacrificed to cut out the back skins for H&E staining.

ASSOCIATED CONTENT

Supporting Information

Additional supporting information, including morphology of CuI nanoparticles coated on N95 mask, EDX elemental mapping of coated cotton fabrics before rinsing with water, EDX spectrum

of CuI-coated cotton fabrics, digital photograph of experimental setup for tensile strength measurement, brief illustration of the plaque assay procedures, quantification of the CuI nanoparticle loss after washing, FESEM image of CuI-coated cotton fabrics after post-treatments, morphology of bacterial cells on coated cotton fabric, and details of post-treatment conditions.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing interest.

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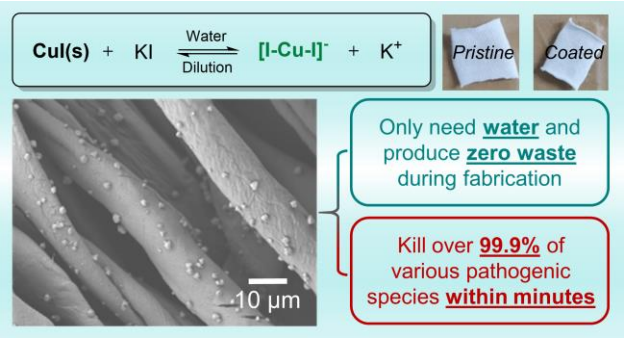
SYNOPSIS

A water-mediated sustainable and scalable approach is demonstrated to *in situ* fabricate CuI nanoparticles on flexible cotton fabrics, affording a durable, skin-compatible, and highly potent antimicrobial coating with rapid germicidal kinetics.



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