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Recent advances in copper and copper-derived materials for antimicrobial resistance and infection control

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Abstract

Antibacterial properties of copper have been known for ages. With the rise of antimicrobial resistance (AMR), hospital-acquired infections, and the current SARS-CoV-2 pandemic, copper and copper-derived materials are being widely researched for healthcare ranging from therapeutics to advanced wound dressing to medical devices. We cover current research that highlights the potential uses of metallic and ionic copper, copper alloys, copper nanostructures, and copper composites as antibacterial, antifungal, and antiviral agents, including those against the SARS-CoV-2 virus. The applications of copper-enabled engineered materials in medical devices, wound dressings, personal protective equipment, and self-cleaning surfaces are discussed. We emphasize the potential of copper and copper-derived materials in combating AMR and efficiently reducing infections in clinical settings.

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Introduction

Copper is an essential trace element with atomic number 29 and is vital for living organisms. Copper has been used since 9000 BC [1]. Copper's antibacterial activity may be seen in Hppocrates' books from 3000 BC [2] and Ayurvedic literature [3]. Copper was originally documented in the Scopus database as an antibacterial coating material in 1962 [4]. In 2008, the United States Environmental Protection Agency (US EPA) recognized copper and its alloys as efficient antimicrobial surfaces [5], capable of killing about 99.9% of bacteria in 2 h hours.

Copper-impregnated fibers are utilized as fabric disinfectants in hospitals [6]. According to reports, implementing copper in medical facilities decreases healthcare-associated infections (HAIs) [7]. Copper's outstanding contact-killing properties make it useful as a coating material for door handles, bed rails, lavatory surfaces, trays, intravenous (IV) poles, and other items [8]. Copper is also utilized in wound dressings to prevent infections and encourage wound healing [9] and as an antibacterial coating for implant surfaces [10,11] owing to its low-*in vivo* toxicity. Furthermore, based on the efficiency of copper in eliminating the SARS-CoV-2 virus, a copper nanoparticle-based antimicrobial coating is being applied to medical personal protective equipment (PPE) kits [12].

Abbreviations

AMR	Antimicrobial resistance
US EPA	United states environmental protection agency
HAIs	Healthcare-associated infections
IV	Intravenous
nZH-Cu	Zeolite doped with copper ions
LMCu	Gallium liquid metal copper alloy
NPs	Nanoparticles
NRs	Nanorods
NCs	Nanocubes
NSs	Nanospheres
ROS	Reactive oxygen species
IUDs	Intrauterine devices
TEM	Transmission electron microscope
PVA	Polyvinyl alcohol
CS	Chitosan
Cu-F	Copper-containing nanofiber (Cu-F)
PPE	Personal protective equipment
CuO	Copper oxide
RT-PCR	real-time polymerase chain reaction
PAN	Polyacrylonitrile
CGHM	Collingwood general and marine hospital
WHO	World health organization
LOC	lab-on-a-chip
EPD	Electrophoretic deposition
ZOI	Zone of inhibition
PP	Polypropylene
SWCNTs	Single-walled carbon nanotubes

This review provides a comprehensive overview of the literature on various copper and copper-derived materials, including metallic copper and copper ions, copper alloys, Cu composites, and various copper nanostructures (Cu NPs, CuS NPs, Cu_2O-Cu NPs, CuO nanorods, Cu-chitosan NPs, and so on), etc. as effective antimicrobial agents. The goal is to highlight various copper-based chemical compositions with outstanding broad-spectrum antibacterial capabilities. We discuss various applications of copper-derived materials in biomedical domains such as wound dressings, medical implants, intrauterine devices (IUDs), PPEs, and self-cleaning surfaces, with the most recent literature receiving the highest importance (last 5 years). Given the current COVID-19 pandemic scenario and the shortest recorded viable period of the SARS-CoV-2 virus on Cu surfaces, a specific section is devoted to showcasing the efficiency of copper and derived materials against COVID-19. The section biocompatibility and cytotoxicity assessment of copper and copper-derived materials in the supplementary information discusses the *in vitro* and *in vivo* toxicity of copper. Figure 1a summarizes various biomedical applications of copper and copper-derived materials as antimicrobial agents and their prospects. Figure 1b shows the timelines of key events in the history of copper as an antimicrobial agent.

Metallic copper and its ions as antimicrobial agents

Research on copper as an antimicrobial agent acquired momentum when U.S. EPA reported 300 surfaces of copper having effective antimicrobial properties [5]. In particular, Seo et al. [23] recorded a 99.99% reduction of *Escherichia coli* and *Staphylococcus aureus* on surfaces coated with 48% copper over a 24-h incubation time. Specifically, Zeolite doped with copper ions (nZH-Cu) showed the effective killing of *E. coli* and *S. aureus* strains [24]. In a concurrent study, Wheeldon et al. [25] compared the viability of *Clostridium difficile* on copper and stainless steel surfaces, which are commonly used in hospitals. Interestingly, Benhalima et al. [26] recorded the destruction of all the vegetative cells of *C. difficile* on the copper surface within 30 min ($p < 0.005$), while stainless steel showed no antibacterial action. In a detailed and comprehensive study, the antimicrobial effectiveness of metallic Cu is assessed against 25 distinct nosocomial bacterial strains (16 *Enterobacteriaceae*, 5 *Staphylococci*, and 4 *Pseudomonas*) isolated from healthcare units in Algeria, 400 g/mL Cu inhibited the growth of 60% of the isolated strains of *Staphylococci*, 25% of *Pseudomonas*, and 43.75% of *Enterobacteriaceae*.

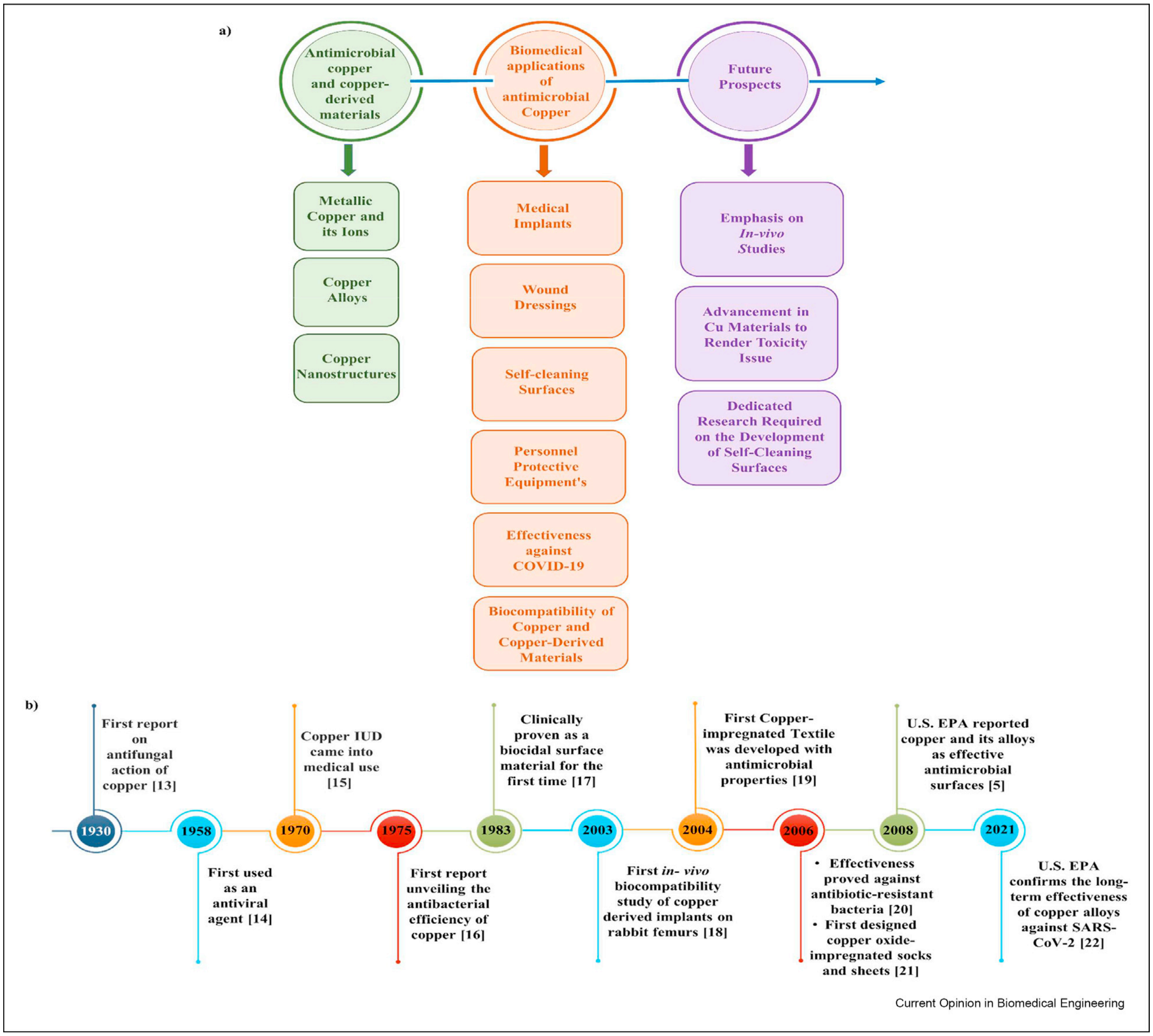
Copper alloys as antimicrobial agents

Copper alloy surfaces have excellent antimicrobial properties against a wide variety of microorganisms. in observational research done from 2015 to 2016 at Reims University Hospital in France, Zerbib et al. [27] discovered that copper alloy successfully reduced the incidence of hand-transmitted healthcare-associated infections. Furthermore, Sheridan et al. [28] demonstrated a novel antiviral fabric infused with gallium liquid metal copper alloy (LMCu) as a breakthrough in the global fight against COVID-19 by demonstrating its applicability in designing PPE for healthcare personnel, bed/bath sheets for hospital settings, and patient clothing. Laourari et al. [29] have studied the antibacterial and antifungal properties of a NiCu-PANI/PVA quaternary nanocomposite against several nosocomial infections. The large zone of inhibition (ZOI) values of more than 17 mm, were recorded for all the tested strains including *E. coli*, *Klebsiella pneumonia*, *Proteus* sp., *S. aureus*, *Fusarium oxysporum*, etc., suggesting their strong antimicrobial potential.

Copper nanostructures as antimicrobial agents

The antimicrobial action of metal nanoparticles (NPs) has been attributed to their high surface-to-volume ratio and size. Sharma et al. [30] investigated the efficacy of antibacterial Cu NPs against *E. coli* and *Proteus vulgaris*. The interaction of Cu NPs with the bacterial cell wall

Figure 1



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(a) Schematic showing the biomedical applications of copper and copper-derived materials as antimicrobial agents and their future scope. **(b)** Timeline of the significant historic events of copper as an antimicrobial agent. This figure includes references [13–22].

causes oxidative stress caused by reactive oxygen species (ROS) that lead to bacterial cell death. In addition, Ha et al. [31] discovered that after a 10 and 30 min exposure to H1N1 virus with Cu NPs, there was no detectable viral DNA, and the contamination of the Cu NPs-treated H1N1 virus was greatly decreased. In another study, Qamar et al. [32] evaluated the antibacterial efficacy of CuO nanorods (CuO NRs) against a series of gram-positive and gram-negative bacterial strains by calculating ZOI which was significant in comparison to the standard drug ($p < 0.0001$) (Supplementary Table S1). Further, Alshareef et al. [33] reported that when *E. coli* was treated with 50 - 2500 μg copper nanospheres (Cu NSs), its growth was hindered within 4 h, while *Enterococcus* sp. growth was inhibited in 2 h except at the highest concentration. On incubation with a similar concentration of copper nanocubes (Cu NCs), the *E. coli* growth was hindered in 24 h, whilst the *Enterococcus* sp. growth was inhibited within 2 h, only for lower concentrations [33].

Mechanism of antimicrobial action of copper

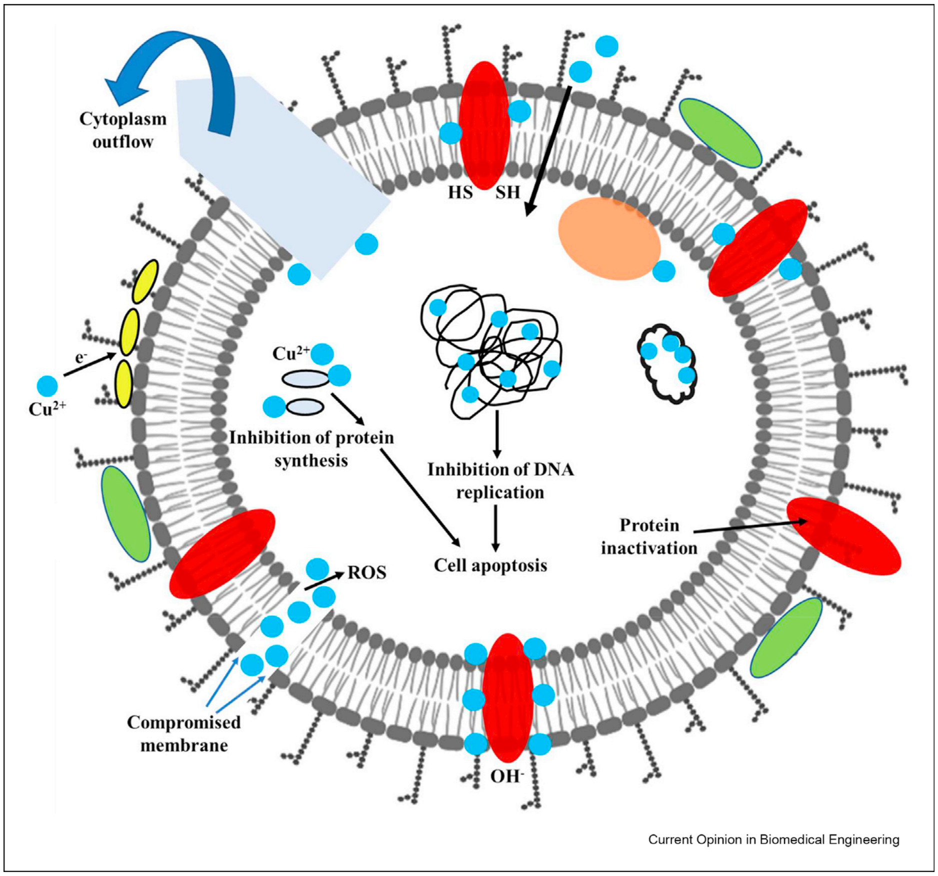
The cell membrane of the bacteria is the primary target of copper antimicrobial action [34]. The electrostatic interactions of copper ions (Cu^{+} and Cu^{2+}) with electronegative groups on the bacterial cell membrane, such as thiol or carboxyl, cause the membrane to rupture [35]. The affinity of thiol for Cu^{+} and the tendency of Cu^{2+} to form reactive oxygen species (ROS) further damages cell proteins, and lipids, and eventually destroy all the genetic material, resulting in cell death [36–38]. Figure 2 depicts the possible antimicrobial action mechanism for copper.

Biomedical applications of copper and copper-derived materials

Medical implants

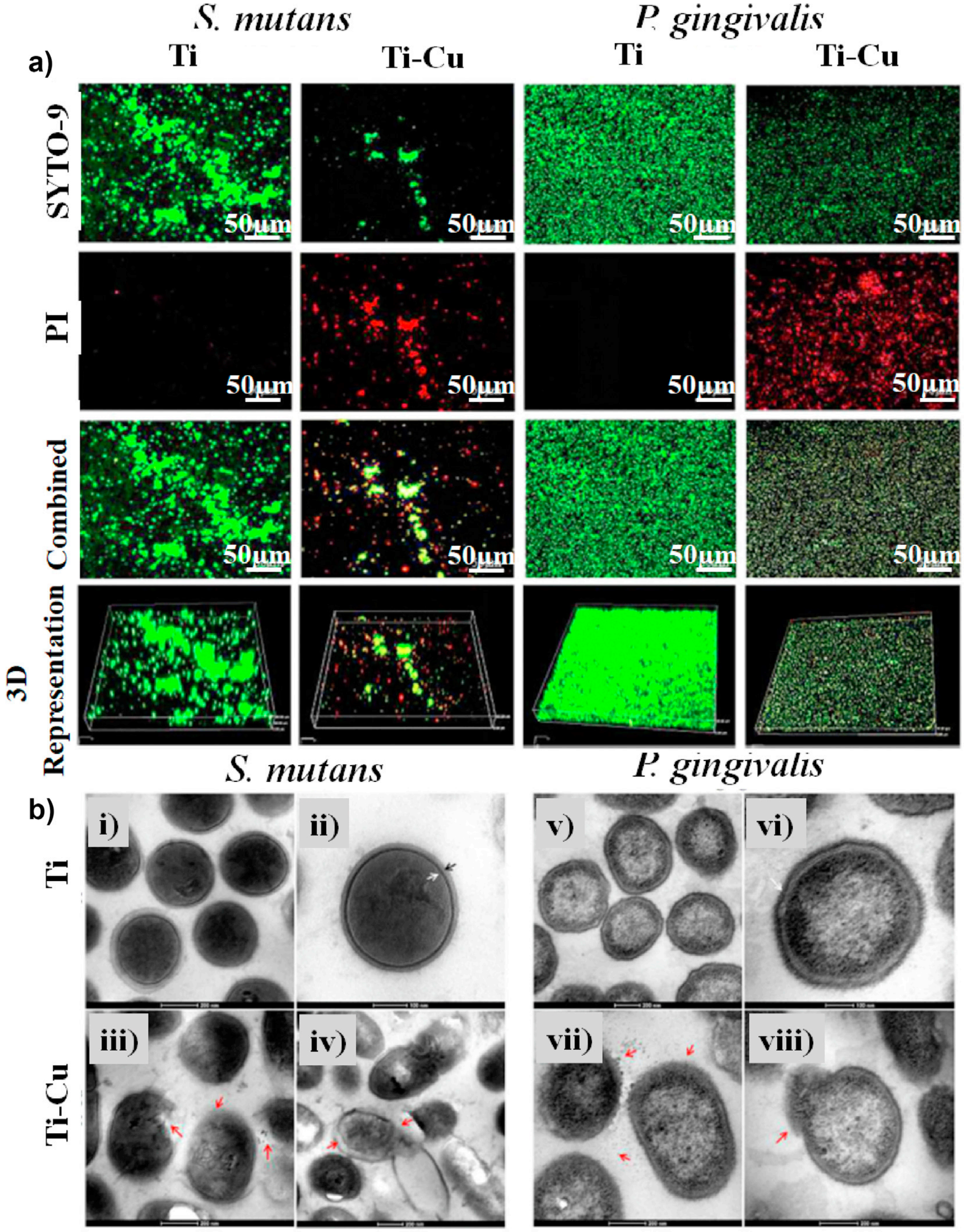
Copper in medical equipment [39] is considered safe for humans, as evidenced by the widespread and long-term use (> 10 years) of copper intrauterine devices (Cu IUDs) by millions of women. Copper nanoparticles coated on the therapeutic caps of dental implants have been demonstrated to inhibit pathogen and biofilm formation [40]. Copper-incorporated titanium (Ti-Cu) alloy implant was also discovered to exhibit excellent antimicrobial properties [41]. It is also been reported by Liu et al. [42] that Ti-Cu alloy prevents peri-implant infections while being biocompatible. The application of Ti-Cu alloy as a modern dental implant to avoid the formation of biofilm of *Streptococcus mutans and Porphyromonas gingivalis* on the surface of dental implants is of great help. In comparison to Ti, confocal microscopy images for 24 h revealed a substantial reduction in the viability of *S. mutans* and *P. gingivalis* biofilm on the surface of Ti-Cu alloy (Figure 3a). Under transmission electron microscope (TEM), both microbes in contact with the surface of Ti-Cu alloy showed disrupted membranes and irregular and reduced ion concentrations in the cytoplasm, while microbes in contact with the surface of Ti alloy showed regular morphologies with the preserved membrane (Figure 3b). In another study, Gollwitzer et al. [43] developed a copper incorporated titanium coating that proved cytocompatibility and antibacterial activity against clinically isolated strains of *S. aureus* and *Staphylococcus epidermidis*. Also, Bergemann et al. [44] demonstrated the effective killing of all *S. epidermidis* strains on titanium-copper-nitride (TiCuN) coated orthopedic implants within 24 h of incubation. Further, Milan et al. [45] developed copper-enhanced carbon coatings on a titanium alloy for bone implants that showed an osteogenic and angiogenic response. After incubating the bacterial strain of *P. gingivalis* for 72 h, biofilm formation was significantly

Figure 2



Schematic illustration of contact killing action mechanism of antimicrobial copper.

Figure 3



(**a**) Fluorescent images and 3D depictions of the growth of biofilm of *S. mutans* and *P. gingivalis* on the surface of Ti and Ti-Cu after incubating for 24 h at 37 °C, (**b**) TEM pictures of *S. mutans* (i–iv) and *P. gingivalis* (v–viii) incubated on Ti (i, ii, v, vi) and Ti-Cu (iii, iv, vii, viii) surfaces. The peptidoglycan layer is marked by white arrows, the cytoplasmic membrane is marked by black arrows, and the disrupted cell membrane is highlighted by red arrows [42]. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

reduced, thus improving the efficacy of such implants. Also, the effect of Cu-TiO_2 coating on Ti was reported in another study performed by Wang et al. [11]. The *in vitro* study proved coating to be cytotoxicity-free and can stimulate the growth, attachment, and differentiation of MC3T3-E1 cells. *In vivo* tests demonstrated that the coating can improve osteogenesis and trigger the formation of new bone. Furthermore, Shahid et al. [46] compared the effectiveness of preventive methods and the possibilities of various copper coated titanium implants in reducing infections associated with implants.

Wound dressings

Lemraski et al. [47] examined the antibacterial efficacy of polyvinyl alcohol/chitosan/copper nanofibers (PVA/CS/Cu NPs) produced by electrospinning against gram-negative and gram-positive bacteria. The nanofiber showed good antimicrobial effectiveness against *Bacillus cereus*, as well as *S. aureus*, *E. coli*, and *Pseudomonas aeruginosa*. In another study, Ahire et al. [48] assessed the ability of wound dressing materials made of copper-containing nanofiber (Cu-F) against the development of biofilm of *S. aureus* (Xen 30) and *P. aeruginosa* (PA01). In the presence of Cu-F, the growth of PA01 and *S. aureus* Xen 30 was reduced by about 13% and 31%, respectively. Also, in the presence of Cu-F, the survival of MCF-12A breast epithelial cells was greatly reduced. Based on the study it was concluded that copper-containing nanofibers are safer to be applied as wound dressing material.

Personal protection equipment (PPEs)

The World Health Organization (WHO) recommends face masks as a preventive measure to reduce SARS-CoV-2 transmission [49].In this context, Hewawadugea et al. [50] demonstrated that copper sulfide (CuS) impregnated three-layered masks are extremely effective in selectively deactivating encapsulated viruses such as SARS-CoV-2 in $<$ 30 min, although Cu^{2+} ions produced from $CuSO_4$ did not exhibit substantial viral suppression. CuS' selectivity for killing encapsulated viruses indicated that CuS may cause physical damage to the viral envelope through physical interactions. The mask completely stops virus-containing droplets from penetrating during short exposure intervals of 1-2 min, while a long-term exposure period of 5-10 min results in an 80% efficiency. Furthermore, Hashmi et al. [51] integrated copper oxide (CuO) onto polyacrylonitrile (PAN)-based electrospun mask membranes and showed its good antibacterial efficacy against a variety of gram-negative and gram-positive microorganisms. It was discovered that increasing the concentration of CuO resulted in a progressive rise in the inhibition zone for all types of tested bacterial strains. Further, Jung et al. [52] evaluated the antiviral activity of copper-coated polypropylene (PP) filters surrounding the KF94 face mask by exposing Vero cells to the coated PP filters after incubating them with the SARS-CoV-2 virus. According to RT-PCR and immunofluorescence, the copper-coated filters suppressed viruses by 75% within 1 h of incubation time. On the spun-bound PP filters, Paranthaman et al. [53] created a chemically bonded organosilane quaternary ammonium chloride-based GS75 coating on spun-bound PP filters and observed sustained deactivation of alpha and beta forms of COVID-19 virus after 72h incubation. Further, Soni et al. [54] also showed that single-walled carbon nanotubes (SWCNTs) modified hydrophobic PP surgical masks were successful in killing 99.99% and 99% of *E. coli* and virus-like particles, respectively.

Self-cleaning surfaces in clinical settings

Nosocomial or hospital-acquired infections are a global problem that causes significant death and morbidity [55]. In a clinical controlled investigation, Mohammady et al. [56] examined the bacterial burden on copper coated and non-coated copper surfaces in a regular ICU in Iran. Copper-coated heavily contacted surfaces decreased the bacterial load by 96% when compared to the control surfaces. In another study by Colin et al. [57], copper alloy door handles and handrails were mounted in 50% of 5 French long-term healthcare centers. The findings show that copper surfaces are less vulnerable to these severe contamination concerns, with the prevalence of these infections reduced by 50% and 79% on copper handrails and door handles, respectively. The copper handles retain their efficacy against the bacteria after 3 years of daily use in healthcare centers, with a bacterial reduction of ~90% for almost all of the examined copper door handles. Collingwood General and Marine Hospital (CGMH) of Canada have created self-sanitizing rooms employing copper-infused panels in patient rooms to inhibit the growth of microorganisms, according to a study [58]. The implementation of copper-infused sanitizing procedures in the hospital resulted in outstanding swab test findings. Previously, the bacterial count under typical settings ranged from 7000 to 8000 colonies, but it has now dropped dramatically to the range of 30-50 colonies.

The antibacterial potential and longevity of a copper-based surface are strongly dependent on the coating deposition process, which modulates surface attributes such as roughness, wettability, adhesion strength, chemical reactivity, and so on. Bharadishettar et al. [59] addressed several coating processes such as thermal spray (TS), electrophoretic deposition (EPD), chemical vapor deposition (CVD), physical vapor deposition (PVD), and others, emphasizing their impact on various surface factors that might influence the antimicrobial efficiency of copper surfaces. The TS technique is a widely used method for producing copper coatings having thicknesses ranging from 20 μm to a few mm with strong corrosion and adhesion strength while being inexpensive. The most prevalent TS techniques are plasma spraying, wire arc spraying, flame spraying, and cold spraying. Champagne et al. [60] showed the higher antibacterial potential of cold sprayed coatings due to greater dislocation density and enhanced copper ion diffusivity provided by sprayed particle impact velocity. Hadzhieva et al. [61] recently investigated the advantages of the EPD technique for depositing bactericidal smart coatings on medical implants, which are based on unique targeted responses, multiple therapeutic effects, and self-cleaning capabilities, which may lead to new antimicrobial treatment possibilities. Varghese et al. [62] discovered that Cu-SiO_2 coatings created by chemical vapor deposition show outstanding antibacterial efficiency against highly resistant bacterial strains such as Vancomycin-resistant Enterococcus coli. The increased antibacterial capabilities are attributed to Cu nanostructuring in the silica matrix of the obtained coatings. The PVD approach is particularly successful in creating nano-thick copper coatings (35 nm-150 nm) with outstanding hardness and thermal stability, and it has been found to improve the antibacterial effectiveness of the surfaces [63].

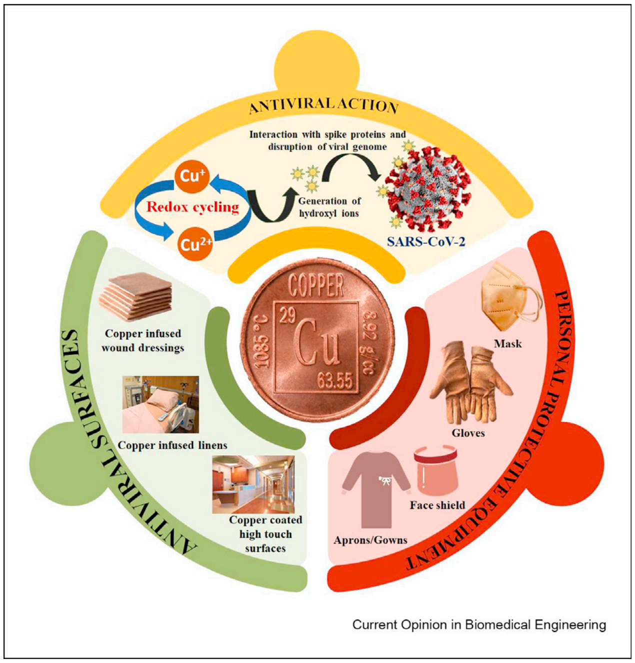
Effectiveness of copper and copper-derived materials against COVID-19

Since the discovery of SARS-CoV-2 in December 2019 [64], the virus has spread rapidly over the world, and the devastating effects of the COVID-19 pandemic continue. As of now, there have been 5 million confirmed cases of COVID-19 globally, according to WHO [65]. SARS-CoV-2 is typically transferred by inhalation of respiratory aerosols [66], direct contact with an infected hand, or indirect transmission through contaminated ambient surfaces, particularly high-touch surfaces [67]. Many studies have been conducted to investigate the long-term infectious persistence of SARS-CoV-2 on various substrates. The US EPA also confirmed the long-term effectiveness of certain copper-derived materials against SARS-CoV-2 [22]. According to a recent report, Doremalen et al. [68] found copper to be more efficient than stainless steel in limiting SARS-CoV-2 survival. According to the scientists, exposing a COVID-19 virus to a copper surface reduces its half-life by 0.774 h (CI = 0.427 to 1.19) and after 4 h, the virus's viability is zero. A CuS-incorporated mask is also extremely efficient in destroying SARS-CoV-2 after only 30 min of exposure [50]. The three-layered mask entirely prevents virus-containing droplets from entering after 1–2 min of exposure, and it is 80% effective after 5–10 min of exposure. In another investigation, Behzadinasab et al. [69] discovered that infection from SARS-CoV-2 suspended in 5 μL droplets deposited on the coating was likewise suppressed by the created CuO layer. When compared to glass, SARS-CoV-2 infectivity in the CuO film is reduced by ~99.9% in 60 min. Furthermore, after 1 h, cuprous oxide (Cu_2O) particles linked with polyurethane, which were designed to inhibit SARS-CoV-2 survivability on solids, reduced the virus titer by 99.9% [70]. Figure 4 depicts copper's potential as an early antiviral weapon against coronavirus.

Future prospects and conclusions

In many public and clinical settings, copper is utilized to reduce microbial contamination on high-touch surfaces. However, to deploy this copper-based antimicrobial coating technology on a large scale, the feasibility of replacing all current contamination-prone surfaces with copper, as well as their antimicrobial durability and cost of replacement, must be addressed. The majority of the research published to assess the antibacterial capability and toxicity of copper and copper-derived materials has been done *in vitro*; nevertheless, it is equally important to encourage *in vivo* settings to validate their application in specialized biomedical fields such as drug delivery, wound dressings, bioimplants, and so on. Alternative testing in a dynamic microenvironment, such as the lab-on-a-chip (LOC) approach, should be researched in addition to traditional *in vitro* testing to provide reproducible, long-term experimental findings with standardized validation. There is significant proof that nanostructured copper coatings are very effective in inhibiting various microbes, and have also evolved as a valuable class of nanomaterials, for a variety of applications in the medical, ecological and industrial fields. Bharadishettar et al. [59] addressed several coating techniques such as TS, CVD, PVD, EPD, and so on, and highlighted various aspects of coated surfaces that lead to increased antimicrobial efficiency. More such research is needed to study the effect of technical parameters on the antimicrobial potential of copper-based coatings. Tiwari et al. [71] explored the development of nanomaterials-infused PPE kits with high hydrophobic characteristics that can serve as an effective barrier to aerosol-mediated viral transmission, which is presently the most likely infection pathway. Several studies have shown the broad-spectrum antibacterial properties and

Figure 4



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Copper's potential as an antiviral weapon against the COVID-19 pandemic.

antiviral efficiency of copper nanostructure-based coatings; nevertheless, the worry with the nanostructured coating is its toxicity, which may be damaging to the environment and living species. To reduce its toxicity to a non-significant level, innovative research methodologies, and inventions for optimizing the toxicity factors that may impede toxicity pathways should be developed. For example, innovative work should be designed to reduce the toxicity of Cu nanostructures by tuning their size, surface functionalization/modification, designing Cu alloy nanostructures, adopting appropriate coating techniques, and so on [72]. Employing a synergism approach, the development of advanced nanocomposites of Cu nanostructures with biocompatible antimicrobial polymers (chitosan, polydopamine, polyethyleneimine), antimicrobial peptides (epsilon polylysine) provide another futuristic strategy to design safe and effective antimicrobial coatings. Overall, copper and copper-derived materials are undeniably effective antimicrobial agents with promising biological applications.

Author contribution statement

CD strategized the review outline. NB, CD, ND, VM, and AKY contributed to writing the article. SR, DM, PS, NKV, RL, DPM, and AKS provided their constructive inputs to improve the quality of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

The authors declare no competing financial interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cobme.2022.100408.

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