



# Antiviral properties of copper and its alloys to inactivate covid-19 virus: a review

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Received: 26 April 2021 / Accepted: 6 August 2021 / Published online: 16 August 2021  
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**Abstract** Copper (Cu) and its alloys are prospective materials in fighting covid-19 virus and several microbial pandemics, due to its excellent antiviral as well as antimicrobial properties. Even though many studies have proved that copper and its alloys exhibit antiviral properties, this research arena requires further research attention. Several studies conducted on copper and its alloys have proven that copper-based alloys possess excellent potential in controlling the spread of infectious diseases. Moreover, recent studies indicate that these alloys can effectively inactivate the covid-19 virus. In view of this, the present article reviews the importance of copper and its alloys in reducing the spread and infection of covid-19, which is a global pandemic. The electronic databases such as ScienceDirect, Web of Science and PubMed were searched for identifying relevant studies in the present review article. The review starts with a brief description on the history of copper usage in medicine followed by the effect of copper content in human body and antiviral mechanisms of copper against

covid-19. The subsequent sections describe the distinctive copper based material systems such as alloys, nanomaterials and coating technologies in combating the spread of covid-19. Overall, copper based materials can be propitiously used as part of preventive and therapeutic strategies in the fight against covid-19 virus.

**Keywords** Covid-19 · Copper · Copper nanomaterials · Antiviral · Antimicrobial · Virus inactivation

## Introduction

Respiratory pathogens kill more people than any other infectious agents every year all around the world (Warnes et al. 2015). Bronchitis, flu, pneumonia, and acute respiratory distress syndrome are all generated by respiratory viruses, which can range from minor respiratory tract infections to life-threatening pathologies (Lee 2017; Warnes et al. 2015). The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which is declared as a pandemic by the World Health Organization (WHO), is one of the deadliest infectious diseases in recent history (Morens and Fauci 2020). It accounts for about 198.7 million confirmed cases and about 4.2 million deaths globally as of 4th August 2021 as reported by WHO (World

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Health Organization 2021). Based on phylogenetic observation, the coronavirus has been formally identified as SARS-CoV-2 by the International Committee on Virus Taxonomy (Sironi et al. 2020). The covid-19 virus was reported initially in December 2019 at Wuhan, China and has transmitted worldwide since then (Doremalen et al. 2020; Zheng 2020). The virus is believed to have started as an animal coronavirus, and has later modified to spread from individuals to individuals. Since the virus is highly contagious, its rate of transmission in the human population is growing and it continues to exist as a global pandemic (Sironi et al. 2020).

Covid-19 virus is a very infectious virus which can be transmitted from a person to another in a number of ways and its spread primarily occurs via respiratory droplets either directly or indirectly (Scully 2020). A person can be directly infected from an infected person within a near vicinity of one meter (Agrawal and Bhardwaj 2021). When a person who is infected talks, coughs or sneezes to exhale droplets, these droplets may fall on the person's surroundings, such as objects and surfaces (Scully 2020). In the other case, a person can become infected indirectly by contacting an object surface, which is contaminated by infected droplets. Direct transmission can be reduced to a certain extent by maintaining social distancing and using masks (Dzisi and Dei 2020). The indirect transmission can be controlled by minimizing the life expectancy of covid-19 virus on contaminated surfaces by developing efficient surface technologies for virus inactivation (Xiling et al. 2021).

Recently it has been discovered that surface exposure plays an important role in the spread of several diseases than previously thought (Otter et al. 2013). The period of time a virus can live is determined by a number of parameters, including the type of surface, temperature, relative humidity, virus strain type, and room ventilation (Chan et al. 2011). In spite of any direct correlation between temperature variation and virus viability, several studies have reported that the period of persistence is shorter at temperatures higher than 30 °C (Kampf et al. 2020). Riddell et al. reported a drastic reduction of virus survivability to less than 24 h on several surfaces at an elevated temperature of 40 °C (Riddell et al. 2020). Many pathogens can survive for months on surfaces. This not only surges the chances of viable microorganisms spreading infection, but it also enhances the

chances of genetic transfer between microbes, which could lead to antibiotic resistance spreading (Warnes and Keevil 2011). After a surface has been infected, it can be spread to seven or eight other clean surfaces by people contacting those surfaces, implying that the materials with inherent antimicrobial activity can aid in preventing further contamination (Noyce et al. 2007). In addition, weak cleaning solutions can leave particles behind, which can lead to infection. The use of antimicrobial surfaces will assist in minimizing the occurrence of infections transmitted by touching infected surfaces. Such contamination of surfaces and transmission of infectious viruses are common factors leading to respiratory disease symptoms (Warnes et al. 2015). As a result, the viral transmission may occur via contamination of regularly touched surfaces in healthcare facilities (Kampf et al. 2020). In a clinical setting, contaminated surfaces may be a cause of hospital-acquired infection (Warnes and Keevil 2011). Within 1 min of contact, surface antimicrobial action with 0.1% sodium hypochlorite or 62–71% ethanol greatly reduced the infectivity of virus. Covid-19 is predicted to have a similar effect (Kampf et al. 2020).

Covid-19 virus can survive on a number of surfaces from hours to days, which is one of the key reasons for which the viral spread is still continuing. The virus can live for hours to days on various metal, glass or plastic surfaces. The covid-19 virus was observed on plastic and stainless steel surfaces for up to three days, according to recent studies by van Doremalen et al. (Doremalen et al. 2020). In the case of a cardboard surface, no viable virus detection was observed after one day. Most interestingly, this study found that the viability of covid-19 virus was completely eliminated within 4 h on a copper (Cu) surface (Doremalen et al. 2020; Suman et al. 2020). In another study, paper and polymer currency displayed covid-19 virus viability to at least 28 days at 20 °C (Riddell et al. 2020).

Covid-19 virus which caused the latest pandemic, is particularly sensitive to copper and its alloy surfaces (Doremalen et al. 2020). With its antimicrobial properties, copper surfaces can be seen to contribute significantly to the control of infections. As a result, usage of antimicrobial metallic copper surfaces is capable of defending infectious microbes by limiting the spread caused by surface contamination (Grass et al. 2011). On copper, as well as a range of copper–zinc and copper–nickel alloys, the virus can

easily be inactivated (National Academies of Sciences 2020). Copper is an important mineral that is necessary for a variety of biological processes. In healthy human beings, the vast majority of copper is directly linked to proteins or to enzyme prosthetic groups (Gaetke et al. 2014). Compounds which contain copper have been used as antimicrobials since ancient Egyptian and Roman civilizations (Morrison 2020). Copper alloy surfaces are presently used in hospitals to reduce the extent of hospital-borne infections, and copper-based compounds are being developed to treat human fungal infections and to protect crops from fungal and bacterial pathogens. Animals possess inherent mechanisms for using copper as a defence against microbes (Besold et al. 2016). Copper is thus considered to play a significant role in the growth and maintenance of immune system (Percival 1998).

Copper can be an effective tool in the fight against covid-19 and future pandemics for a number of reasons (National Academies of Sciences 2020). These alloys can be commonly used in public spaces on common touch surfaces, particularly in areas where there is a lot of human traffic (National Academies of Sciences 2020). While the use of copper for heavily touched surfaces does not remove the necessity for hand washing and sanitization, using copper for countertops, door and cabinet handles, and railings is a passive technique to minimize the time that the viruses can survive on surfaces. This, in turn, will help to reduce the transmission rates in shared spaces and common areas (Grass et al. 2011). Copper surfaces' antimicrobial properties can be integrated with other disinfection methods and a healthcare facility's overall hygiene definition (Grass et al. 2011). For reducing the spread of the virus, copper surfaces play a significant role (Warnes et al. 2015). In view of this, the present review article focuses on the effective role of copper in covid-19 virus control, its underlying mechanism for antiviral activity against covid-19 virus and potential copper-based material systems for covid control.

### History of copper in medicine

Copper is an important micronutrient for almost all living things. The antiviral properties of copper have been known for centuries (Warnes and Keevil 2011). Coppers' antimicrobial properties have been first

recorded in medical texts from Egypt between 2200 and 2600 BC, where copper was used for water sterilisation and treatment of wounds (Hassan et al. 2014). Copper or copper-based derivatives were used by the Romans, Aztecs, Greeks, and others to cure headaches, intestinal worms, infections in ear and for general hygiene (Grass et al. 2011). Copper was an important medicine in ancient Greece, due to its easy availability and medicinal aspects. It was prescribed for the treatment of ulcerations associated with varices. Dry powder of cupric oxide and copper sulphate was mixed and sprinkled on raw wounds to prevent infection. Wounds were treated with honey and red copper oxide mixture as an antiseptic (Konieczny and Rdzawski 2012). In India, the use of Tamra Patra (copper vessels) in numerous pharmacological treatments was recorded by Charaka in his work Charaka Samhita (Galib et al. 2011).

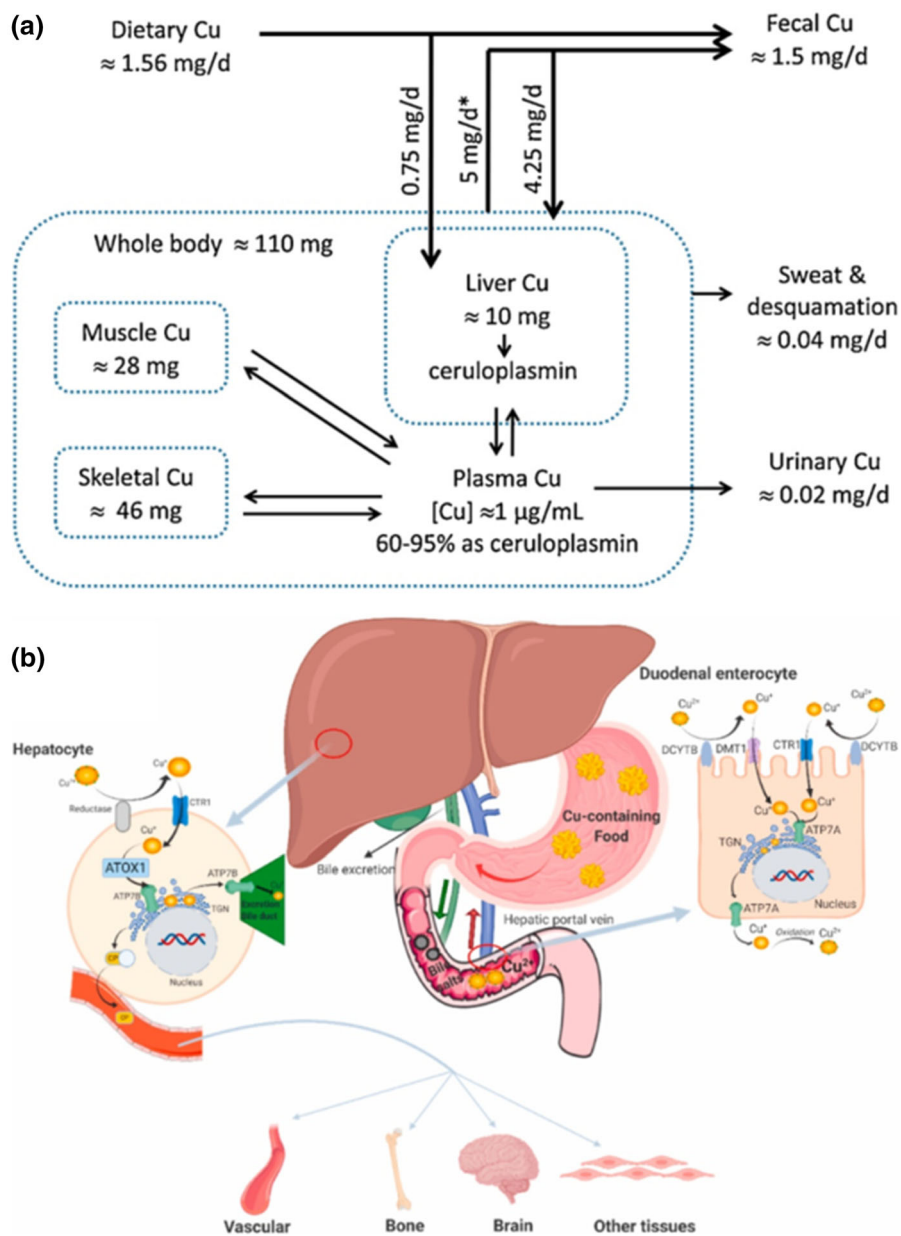
The discovery that persons who work with copper appeared to have immunity against cholera in 1832 and following epidemics in Paris, ignited a new understanding on the medical potency of copper in the nineteenth century. In the nineteenth and early twentieth centuries, various inorganic copper preparations were utilized for the treatment of chronic adenitis, scrofulosis, syphilis, anaemia, impetigo, lupus, chorea, tubercular infections, eczema and facial neuralgia. Copper was used as an antimicrobial agent until 1932 when commercially available antibiotics came to front (Grass et al. 2011). Copper's importance for humans was not recognized before 1928, but recently Martínez et al. (García-Martínez et al. 2021) demonstrated that copper is necessary for erythropoiesis in rat. Copper's value for humans was not confirmed before 1960s, after a study conducted on malnourished Peruvian children. These children had anaemia that would not react to Fe therapy, neutropenia, and bone defects that could be treated with copper supplements (Bonham et al. 2002).

### Effect of copper content in human body

Copper is an important trace element for all aerobic life forms. Copper serves as a cofactor (as a helper metallic ion to assist in biochemical transformations) for many redox enzymes, most importantly for ceruloplasmin, which plays a vital role in the iron metabolism in the body (Bost et al. 2016). In addition

to its role as a cofactor, copper is essential for a multitude of biological functions which encompasses antioxidant defence, neuropeptide synthesis and immune function. The information regarding copper pools and fluxes are provided in Fig. 1 a (Bost et al. 2016). Copper absorption in mammals occurs

predominantly in the small intestine, after digestion in the stomach and duodenum (Gaetke et al. 2014; Nevitt et al. 2012) and copper metabolism in human body is depicted in Fig. 1 b (Wang et al. 2021). Excess copper content as well as its deficiency causes problems in animals (Iakovidis et al. 2011). Since



**Fig. 1 a** Copper absorption by various organs such as muscles, liver and skeletal system and its expulsion via sweat and urine. Reprinted from (Bost et al. 2016), with permission from Elsevier. **b** Copper metabolism inside human body upon

absorption by stomach and small intestine and the mechanism by which copper compounds being transferred to different parts of human body. Reprinted from (Wang et al. 2021), with permission from Elsevier

both deficiency and excess of copper can result in negative health effects, assessing copper specifications and safe limits for intake is difficult. (Gaetke et al. 2014). The deficiency of copper in humans is rare and occurs mostly in people with serious illness who receive copper deficient nutrition intravenously (Raha et al. 2020). In humans, the recommended daily intake of copper is 2.6 mg. However, 0.9 mg is the present daily intake recommendation in the United States (USA Food and Nutrition Board). But according to a dietary report, for adult men even 1.03 mg of copper per day may not be sufficient (Chambers et al. 2010). The proliferation of mitogen cultured lymphocytes was significantly reduced when fed with a low-copper (0.38 mg/day) diet and its IL-2R secretion which in turn affects immunity. These indexes were not restored within 24 days of feeding a high-copper (2.49 mg/day) diet (Percival 1998).

Even though serious copper deficiency is highly unusual in case of humans (Bonham et al. 2002; Hopkins and Failla 1997), it may lead to adverse consequences. It has been reported that maternal copper deficiencies can consequently result in abnormalities associated with various systems such as cardiovascular, pulmonary neuronal, skeletal, immunology and impaired cognitive and behavioural functions in offspring during infancy and beyond (Gambling and McArdle 2004). Copper deficiency was found to lower the resistance towards parasitic infections and T lymphocytes as evident from animal studies. It was found that during copper deficiency, many features of monocyte, neutrophil and T cell function are damaged (Bonham et al. 2002; Minatel and Carfagnini 2000). Immunity is the critical factor in the fight against covid-19 virus and other diseases. The immune system requires copper for a variety of tasks. Several studies have found that deficiency of copper results in a weakened immune response in humans. Copper serves as an important factor for the proper functioning of B cells, T helper cells, natural killer (NK) cells, neutrophils, and macrophages, all of which are essential immune cells. These blood cells are required for fighting against infectious pathogens, cell-mediated immunity, and the generation of pathogen-specific antibodies (Raha et al. 2020).

A wide range of metalloenzymes that catalyse electron transfer reactions depends on its capability to transit between two states of oxidation, CuI and Cu2 (Miyamoto et al. 1998). For many enzymes it is a

cofactor and influences a variety of immune response factors (Besold et al. 2016; Minatel and Carfagnini 2000; Weiss and Carver 2018). Not only copper, but also the copper chelates such as thujaplicin-copper chelates are effective in viral control. During apoptosis, thujaplicin-copper chelates prevent viral production from infected Madin–Darby canine kidney (MDCK) cells. The findings suggest that influenza virus-induced apoptosis was inhibited by copper chelates, and it is not dependent of influenza virus subtype. Copper chelates have anti-apoptotic effects 2–4 h after infection, which shows that in the early stages of apoptosis, copper chelates impact MDCK cells (Miyamoto et al. 1998).

#### Antiviral mechanism of copper against covid-19

Copper's toxic properties make it a powerful antimicrobial agent (Besold et al. 2016). The innate immune system's defensive mechanisms for destroying the pathogen include the production of toxins to resist microbial attack [such as nitrogen species and reactive oxygen species (ROS)], and the withdrawal of nutrients to starve the invading microbes. Copper's ability to generate ROS makes it potentially toxic (Hodgkinson and Petris 2012). Copper presence leads to disruption of the Coccilithovirus lytic cycle, with increased ROS generation (Raha et al. 2020). One of the innate immune system's defense mechanisms is to expose pathogenic bacteria to copper toxin within the host, which is an effective killing mechanism. Influenza A virus particles were significantly reduced on copper surfaces.

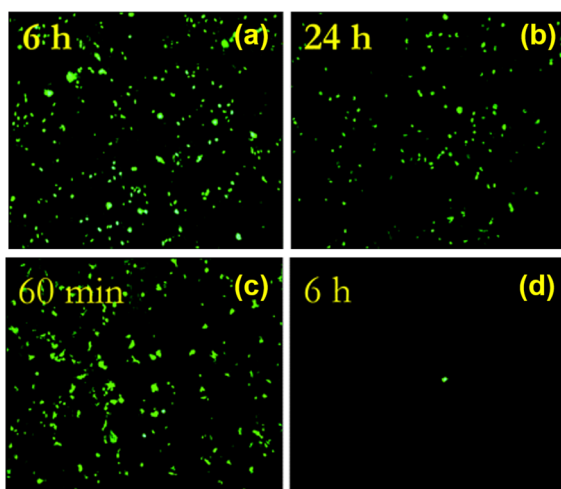
Copper ion binding and cross-linking between the strands of genome will result in the damage of viral genomic DNA (Noyce et al. 2007). Hence an effective inactivation results from the synergistic action of copper ion attack and ROS generation. Copper-containing products possess the ability to minimize the number of microbes in the clinical environment significantly (Casey et al. 2010). Since DNA is a potential target for cytostatic drugs, the copper compounds' effect on DNA functionality is very crucial. The ability of Cu (II) complexes to bind to DNA and its nuclease activity in the presence of reducing agents have long been established. The degradation of DNA is thought to be caused by a Fenton-type reaction in which ROS are generated. Their behaviour is influenced and controlled by the

organic ligand type used in these copper complexes (Iakovidis et al. 2011). Copper destroys microbes by degrading their genomic and plasmid DNA. After a long period of incubation, no live microorganisms were retrieved from surfaces of copper, suggesting that at a rate of at least 7–8 logs per hour, contact killing occurs (Grass et al. 2011). Copper is an effective antimicrobial agent (Grass et al. 2011; Besold et al. 2016; Iakovidis et al. 2011; Ishida 2018). When a virus is exposed to copper surface, the viral nucleic acid degrades as a result of the intervention by copper ions (Iakovidis et al. 2011). One such study conducted by Sagripanti et al. (Sagripanti et al. 1993) found that Cu (II) ions inactivated five enveloped or non-enveloped, single- or double-stranded DNA or RNA viruses and its effectiveness was further improved by the addition of peroxide. Compared to iron (III) ions, the virucidal activity after the addition of peroxide was observed to a larger extent in case of Cu (II) ion suggesting copper peroxide as an effective antimicrobial agent against  $\Phi$ X174,  $\Phi$ 6, Herpes, T7, and Junin simplex viruses. Compared to stainless steel surfaces, copper surfaces showed better antimicrobial behaviour. A study by Noyce et al. (Noyce et al. 2007) investigated the levels of contaminations of influenza A virus after 1, 6, and 24 h exposure time on both copper and stainless steel surfaces. As observed in Fig. 2a, b, the stainless-steel surface displayed a higher contamination level of

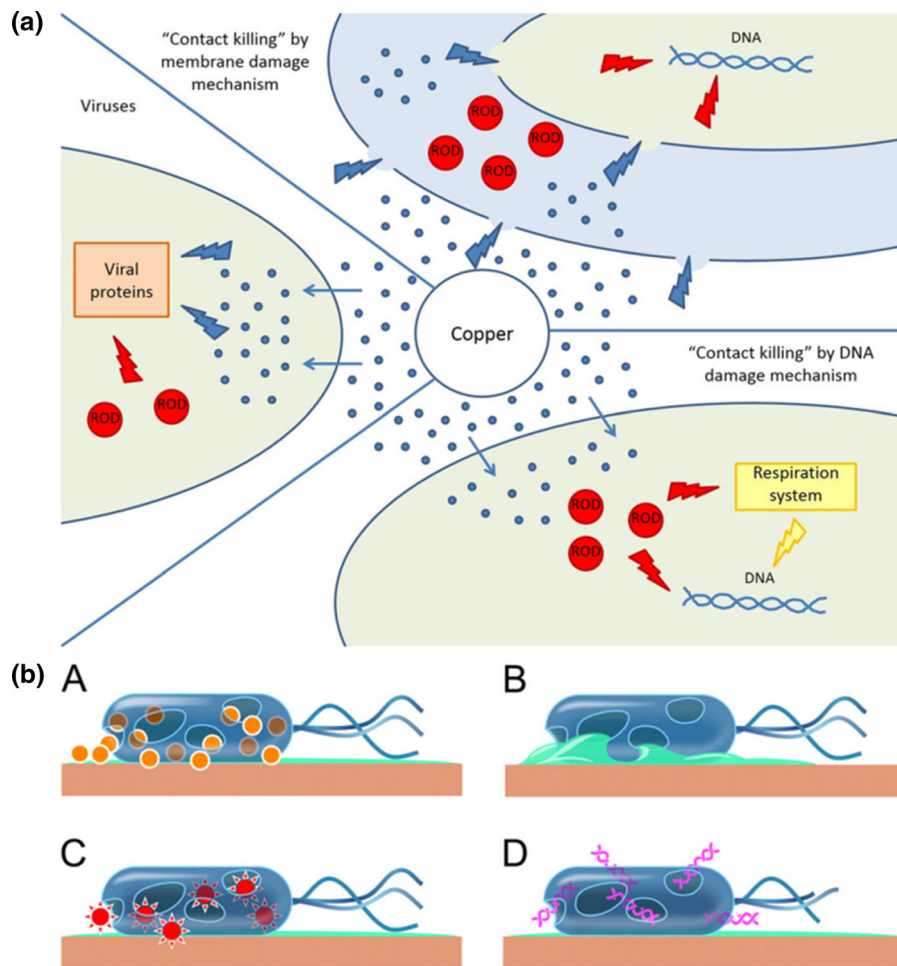
500,000 virus particles even after 24 h incubation time. Whereas, copper surface (Fig. 2c, d) exhibited only 500 virus particles at only 6 h of incubation time indicating its superior antimicrobial property. A similar experiment by Michels et al. (Michels et al. 2015) has observed a significant decrease of 83% bacterial activity on copper alloy surfaces when compared to other materials. On the copper alloy tested, complete loss of infectious activity was achieved even within 5 min of exposure. The inactivation was not only easy, but also followed by the irreversible damage of viral RNA and serious structural damage (Dzisi and Dei 2020). The viral genomes were disrupted by the copper exposure, and the morphology of virus was irreversibly changed, inducing the disintegration of envelope and the dispersal of surface spikes. The inactivation was triggered by Cu (I) and Cu (II) ions, aided by ROS generation on copper alloy surfaces, which led to even faster inactivation as compared to non-enveloped viruses on copper. The contact killing mechanism is schematically depicted in Fig. 3a (Vincent et al. 2018).

One of the mechanisms by which the copper ions help to kill the bacteria is illustrated in Fig. 3b, by Grass et al. (2011). Observations by Grass et al. (2011) and Warnes et al. (2015) suggested that the virus killing mechanism involves “entering” of copper ions into the cell, destroying their DNA, and restricting their metabolism, respiration and reproduction processes. On metallic copper surface, bacteria, viruses and yeast were rapidly killed, which has given rise to the term “contact killing”. The term “contact killing” was coined by Grass et al. (2011) wherein large amounts of copper ions are taken in by the bacteria present on the surface, causing cell damage. After which, the cell membrane gets ruptured inducing the loss of cytoplasmic content present inside the cell. Further, these copper ions cause the generation of ROS which further damage the cell. Other mechanism includes the use of highly thin sheet “with sharp edges” that could penetrate the cell membrane and kill it. Graphene is one such material that has this property. A latest study by Selvamani et al. (2020), also showed that copper surfaces could be treated with laser to create rugged textures thereby increasing its surface area and hence the antimicrobial activity.

Considering the need to eliminate covid-19 virus in surface materials, many studies have researched the effectiveness of copper and its alloy surfaces for



**Fig. 2** Influenza virus infectivity on exposure to (a, b) stainless steel surface and (c, d) copper surface. Reprinted from (Noyce et al. 2007) with permission from Massachusetts Medical Society

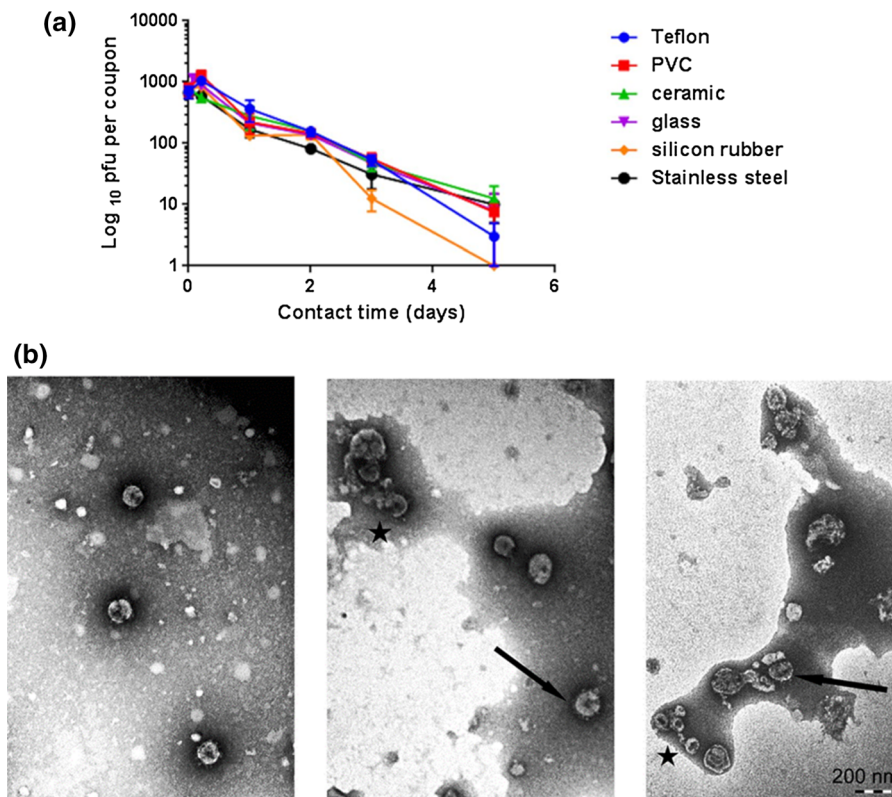


**Fig. 3** **a** Contact killing mechanism of copper against bacteria (top), virus (middle) and fungus (bottom). Reprinted from (Vincent et al. 2018) with permission from Wiley. **b** Illustration of contact killing mechanism on a copper surface (a) rupture of

cell membrane, (b) loss of cytoplasmic content, (c) generation of other ROS by copper ions. Reprinted from (Grass et al. 2011) with permission from American Thoracic Society

virucidal action (Warnes et al. 2015; Doremalen et al. 2020; Michels et al. 2015; Otter et al. 2020). Warnes et al. (Warnes et al. 2015) observed the amount of virus (represented by Plaque forming units, PFU) after certain amount of its exposure to copper ions in copper coupons. In comparison with other materials, brass alloy with greater than 70% copper, exhibited superior virucidal action on HuCoV-229E. There was almost no trace of virus on the surface within a shorter duration of 60 min. On the other hand, other materials commonly used in households such as stainless steel, Teflon, PVC (polyvinyl chloride), glass and ceramics took at least 5 days at room temperature for complete eradication of the virus. Further, the amount of virus to remain in the surface was proportional to the amount

of copper in the alloy, indicating its effectiveness in virucidal behaviour which is shown in Fig. 4. Similar to stainless steel, zinc and nickel alloys exhibited a reduced virucidal action. Recently, Doremalen et al. (2020) conducted a similar study comparing the stability of SARS-CoV-1 and SARS-CoV-2 in plastic, aerosol, cardboard, and stainless steel with copper. The results showed similar effectiveness of copper in antiviral action. Plastic and stainless steel contained SARS-CoV-1 and SARS-CoV-2 virus even after 72 h. However, after 8 h traces of SARS-CoV-1 and after 4 h trace of SARS-CoV-2 was not found on copper surface. Table 1 depicts the comparison of antimicrobial property of copper with other materials. As shown in Fig. 4a, b the number of viruses on surface



**Fig. 4** a. Comparison of virucidal action of different materials b. Covid-19 virus on interaction with stainless steel for 10 min, disintegration of virus after 10 min on a copper surface and

shrinking of virions with surface spike damage after 30 min. Reprinted from (Warnes et al. 2015) with permission from American Society for Microbiology

decreases over time (Warnes et al. 2015). Despite wearing gloves, dentists and other health care personnel are at the risk of infection as they come into close contact with infected patients. Although hygiene is the first line of defence against illnesses associated with healthcare, they can also come in contact with the equipments in the operating room which can cause the spreading of viruses like covid-19 from these contact surfaces. Moreover, these viruses can rapidly spread to other equipments such as dental unit, medical clinic or dental furniture from the primary contaminated surface by surface-skin transfer. (Poggio et al. 2020). It is important to note that during a viral outbreak, orthopaedic trauma services which stay open are at increased risk of the virus spreading from infected patients who are asymptomatic seeking care from orthopaedic surgeons and causing surface contamination (Guo et al. 2020). A solution could be the use of copper shields or coatings on such type of frequently touched surfaces. In fact, covid-19 virus exposed to

copper and its alloy surfaces showed rapid inactivation, irreversible viral RNA destruction, and severe structural damages. Copper alloy surfaces, in combination with appropriate cleaning routines and sound clinical practices, may aid in the control of respiratory virus transmission, such as MERS and SARS (Sagri-panti et al. 1993; Delgado et al. 2011). Due to its efficient antiviral activity, they are used for highly touchable surfaces but disinfectants must be chosen carefully since they can impact antiviral efficacy and durability over time (Bryce et al. 2020).

### Copper based materials in fighting covid-19 virus

Copper alloys must be commonly used in public spaces on common touch surfaces, especially in areas where there is a lot of human traffic. Antimicrobial copper components such as doorknobs, stair railings, push plates, handles, drawer pulls, electrical switch



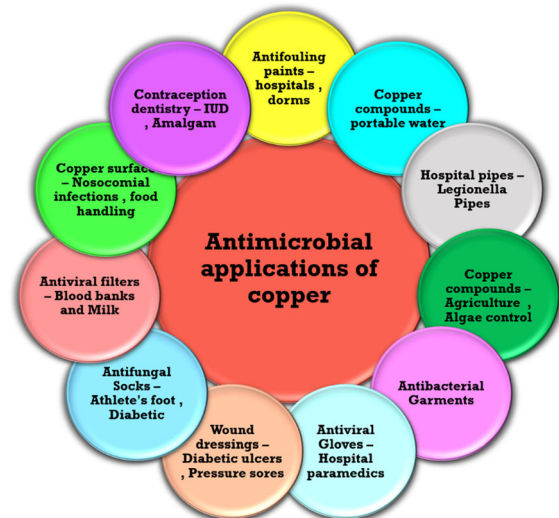
**Table 1** Summary of comparison of antimicrobial property between Cu and various other materials

S. No.	Material	Effectiveness of material compared to copper	Virus tested	Author name and reference
1	Iron-peroxide	The viruses were in, all cases, quite resistant to iron peroxide when compared to metallic Cu peroxide	φ4X174, T7, + 6, Junin, and herpes	Sagripanti et al. (1993)
2	Stainless steel	500,000 virus particles were still infectious and remained up to 72 h after 24-h incubation on stainless steel. While only 500 particles were active after incubation of just 6 h on copper	Influenza	Noyce et al. (2007)
3	Plastic surfaces	Covid-19 virus will linger for 9 days	Covid-19	Warnes et al. (2015)
4	Ceramics	Covid-19 virus will linger for 5 days	Covid-19	Warnes et al. (2015)
5	Glass	Covid-19 virus will linger for 4 days	Covid-19	Warnes et al. (2015)
6	Brass	Covid-19 virus was inactivated in 40 min or less on brasses	Covid-19	Warnes et al. (2015)
7	Nickel	Inactivation was relatively ineffective	Covid-19	Warnes et al. (2015)
8	Silver	Ions releasing from silver prevent replicating of DNA which helps to kill bacteria. But because of the high cost, it is not commonly used	Covid-19	Otter et al. (2020)
9	Cardboard	Covid-19 virus will linger for 24 h	Covid-19	Doremalen et al. (2020)
10	Plastic	Up to 72 h	Covid-19	Doremalen et al. (2020)

plates, plumbing fixtures and sinks, and elevator floor buttons must be properly mounted in public transportation systems, airports, cruise ships, military bases and ships, shopping malls, colleges, hotels, entertainment centres, sports stadiums, large office buildings, hospitals and healthcare facilities, and more. In addition, copper is now used in every part of the pharmaceutical industry, from antiseptic and antifungal drugs for health safety to personal hygiene products. Copper also acts as a surface disinfectant (). Figure 5 shows the present and future applications of copper in various fields requiring antiviral properties.

Copper based alloys

Antibacterial and antiviral materials or surfaces have the ability to regulate healthcare-related diseases, allowing pandemics like covid-19 to be contained to some degree. Copper and its alloys are proved to be an efficient virucidal agent by various researchers around the globe as mentioned in the previous sections (Balasubramaniam et al. 2021). Many different



**Fig. 5** Copper’s biocidal properties have led to existing and possible future uses of copper and its compounds in a variety of fields

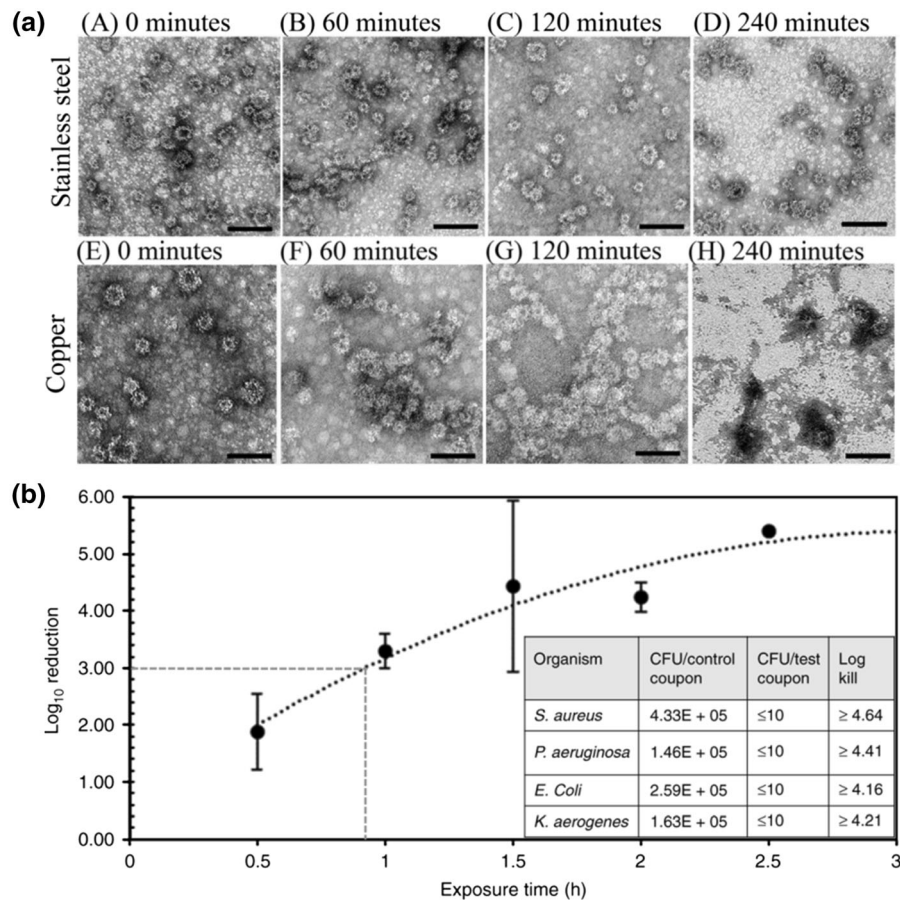
varieties of copper based materials have surfaced proving to be effective in such antimicrobial action. Copper is good at inactivating the virus which are

herpes simplex, bronchitis, HIV-1, hepatitis C, murine norovirus (MNV-1), poliovirus, 44 monkeypox, covid-19 by damaging the biomolecules, RNA, DNA, genome and protein shell (Gauri et al. 2020). Viruses of the same family have identical structures and genomes, implying that they can be regulated and prevented using similar methods. As shown in Fig. 6a, the dwell time of these microbes are observed to be drastically shorter in copper, as compared to the common household materials such as stainless steel (Manuel et al. 2015).

Less than 1.1 log<sub>10</sub> reductions in RNA copy number of HuNoV genome was detected on stainless steel surface after a time of 240 min in comparison to a 2–3 log<sub>10</sub> reduction in span of 60 min on surface having greater than 70% copper (Manuel et al. 2015).

Additionally, it was found that the rate increases with increase in copper content and protein band intensity started to reduce within a period of 5 min. Likewise, copper bearing stainless steel 316L-Cu SS was observed to possess favourable antibacterial property which can be used for the prevention of Implant-related infection (IRI) both in vitro and in vivo (Zhuang et al. 2020). Inactivation of bacteria or viruses on copper, can take minutes or hours depending on whether the pathogens are gram-positive or gram-negative bacteria or enveloped or non-enveloped viruses. (Bryant et al. 2021).

In comparison with pure copper metal, no Murine Norovirus (MNV) was found after 30 min on copper and 60 minutes on copper–nickel and this time duration will vary according to temperature (Warnes



**Fig. 6** Comparison of virucidal properties of copper with stainless steel **a** microbes remaining after 0, 60, 120 and 240 min. Bar, 0.1  $\mu\text{m}$ . Reprinted from (Manuel et al. 2015) with permission from American Society for Microbiology.

**b** Bacterial reduction kinetics on coupons containing copper glass ceramic particles. Reprinted from (Gross et al. 2019) with permission from Springer Nature

and Keevil 2013). Other alloys of copper such as Ti–Cu when used against *Escherichia coli* and *S. aureus* showed better antibacterial rates of 96.8% and 80%, respectively after 12 h and when observed after 24 h reached up to 99%. From scanning electron microscopy images, it was observed that copper could inhibit the bacteria adhesion and decrease biofilm development (Liu et al. 2018). According to another similar research, Ti-10 Cu alloy (containing 10% Cu) showed a 75% reduction of anaerobic porphyromonas gingivalis cell members within 24 h time period (Li et al. 2021). High entropy alloy-based material design enables the advent of innovative and advanced biomaterials (Calin et al. 2021). Copper based high entropy alloy CuFeCrCoNi, possess good corrosion resistance, mechanical properties and antiviral activity which inactivated 99.99% of H1N1 virus in 24 h (Li et al. 2021) indicating the effectiveness of copper ions in the surface of the alloy.

Another copper-based material, calcined copper called as “Tamra bhasma” has been mentioned in Ayurveda to be effective in the fight against similar microbes (Gauri et al. 2020). Tamra Bhasma (calcined copper) with and without Amrutikarana (a special technique to get rid of the remaining qualities that are not acceptable) did not show any signs or symptoms of toxicity at low level but showed some mild toxicity in liver, heart, thymus and kidney on rats. The copper–glass ceramic powder has a good controlled release of copper ions which help to do different actions like the destruction of plasmid DNA, and RNA. With this powder there is reduction of greater than 99.9% in bacterial colony count even at very low surface concentration of copper with around 5% as shown in Fig. 6b (Gross et al. 2019).

### Copper based nanomaterials

Nanotechnology enables distinctive possibilities to solve a wide range of problems in a variety of technological aspects (Ingle et al. 2014). Developments in the field of nanotechnology have opened numerous opportunities in the drug development sector in recent decades. Nanoparticles (NPs) having diameters of less than 100 nm (nm) have drawn tremendous attention in medical analysis, delivery of drugs, and therapeutics (Tavakoli and Hashemzadeh 2020; Rajan and Sahu 2020). As compared to particles fabricated from same substance in higher scales, NPs

possess a higher surface to volume ratio, making them more reactive (Argueta-Figueroa et al. 2014). The NPs are associated with wide surface area which assist in improving their interaction with microbes, thereby allowing them to carry out a broad-spectrum of antimicrobial activities (Ingle et al. 2014). In addition, NPs have specific physical, chemical, and biological characteristics due to the presence of a large fraction of surface atoms. Therefore, a fusion of nanotechnology and biology holds the potential of solving a wide variety of biomedical issues to revolutionize the field of health care (Argueta-Figueroa et al. 2014).

In recent years, a wide range of metal-based NPs have been studied for antiviral activities. Many metal NPs possess potential antiviral effects and these NPs are prospective materials in the treatment of a wide range of viral diseases (Aderibigbe 2017). Another possibility is that resistance to metal NPs would be unlikely to evolve since these NPs will strike a wide variety of targets in the virus (Aderibigbe 2017). Antimicrobial activities of many NPs have been studied against different kinds of human pathogens, which includes fungi, bacteria, parasites and viruses (Tavakoli and Hashemzadeh 2020). Metal NPs have the ability to stop viral replication and propagation, as well as to cause viral inactivation, and induce viricidal effects by blocking the cell virus attachment to the cells and entry of virus into the cells. Destruction of the outer layers of covid-19 virus is one potential way of action of metal NPs against the virus (Uskoković 2020). Antimicrobial function of NPs can be explained by its unique binding to the surface of microorganism and the subsequent metabolism of such materials within microorganisms (Raffi et al. 2010).

Copper has a wide range of biocidal activities and effectively stops bacteria, fungi, viruses, and algae from growing. Copper-based NPs are currently employed to assign biocidal properties to wound dressings and socks (Rubilar et al. 2013). Due to the wide spectrum of antiviral operation of copper ions against the enveloped and non-enveloped viruses, such as herpes simplex virus, influenza virus, MS2 coliphage, and hepatitis A virus, they have been commonly used as antiviral agents (Shionoiri et al. 2012). It is reasonable to conclude that the availability of surface area for interaction determines the binding of copper NPs with microorganisms. Since NPs have a wide surface area, they have a higher killing efficacy compared to larger particles, and can induce

cytotoxicity in microorganisms (Raffi et al. 2010). Against human norovirus copper sulphide NPs have exhibited virucidal effect by capsid protein degradation. Copper NPs in the iodide, oxide, and sulphide forms have shown antiviral activity against herpes simplex virus, human norovirus and H1N1 influenza virus (Raffi et al. 2010).

CuO-NPs have the ability to reduce viral populations and H1N1 virus activity has been reported to be inhibited by copper iodide NPs (Ishida 2018). CuO-NPs are widely used in antifouling paints, agricultural biocides, wood preservation, and antimicrobial textiles due to their exceptional antimicrobial properties (Tavakoli and Hashemzadeh 2020). CuO-NPs possess antibacterial action against gram-negative and gram-positive bacteria of various types (Ingle et al. 2014; Argueta-Figueroa et al. 2014). The key mechanisms of CuO-NPs antibacterial activity are based on the development of ROS, protein oxidation, lipid peroxidation, and degradation of DNA in bacteria. Copper ions released by CuO-NPs possess a direct effect on different targets and cause the development of ROS, resulting in DNA denaturation and damage of cell integrity. CuO-NPs have been linked to strong antiviral activity against HSV-1. The production of ROS by the release of copper ions from the NPs, which plays a vital role in HSV-1 inactivation via viral protein oxidation or viral genome breakdown, is one mechanism hypothesised to explain the antiviral actions of CuO-NPs (Tavakoli and Hashemzadeh 2020).

Antiviral properties of copper iodide (CuI) NPs were tested against the non-enveloped virus feline calicivirus (FCV), which was used as a human norovirus proxy. FCV infectivity to Crandell-Rees feline kidney (CRFK) cells was examined using CuI NPs. It was discovered that treating FCV with 1000 g/ml CuI NPs reduced infectivity to CRFK cells by seven orders of magnitude. CuI NPs with an average size of 160 nm displayed antiviral activity against influenza virus. A virus with a swine origin was discovered utilising a plaque titration experiment. For 60 min of exposure time, the dose-dependent viral activity was determined to be around 17 g/ml, and the 50% effective concentration was also around 17 g/ml. Virus inactivation as a result of viral proteins including neuraminidase and hemagglutinin being degraded by nanosized copper (I) iodide particles. As a result, these NPs could be useful in the creation of face masks, filters, kitchen cloths and protective clothing,

to protect against viral attacks (Ingle et al. 2014). Bacteria contains nanometer-sized pores in their cell membranes, through which the NPs will pass, causing cytoplasm degradation and eventually leading to cell death. The primary antibacterial mechanism is heavy ion adsorption to bacterial cells, which confers antibacterial efficacy in a concentration-dependent manner (Argueta-Figueroa et al. 2014).

Metal NPs have been used as medicinal agents in Ayurveda for hundreds of years. Due to their specific chemical and physical properties, Ayurvedic Bhasma (nano particle), comprising of biologically derived metals and mineral NPs, could evolve as novel antiviral agents against covid-19. (Sarkar and Das Mukhopadhyay 2021). Several Ayurvedic Bhasma preparations are listed as being effective in the treatment of covid-19. Because of the presence of NPs, these formulations are effective when taken sublingually or orally. They have greater bioavailability and absorption. In order to combat covid-19, a variety of Ayurvedic formulations have been suggested for both prevention and treatment. Swarna Bhasma (Au NPs), Rajata Bhasma (Ag NPs), Tamra Bhasma (Cu NPs), Vanga Bhasma (vanadium NPs) and Lauha Bhasma (Fe NPs) are all present in these preparations (Rastogi et al. 2020). Anti-inflammatory drugs are useful in Covid-19 care owing to the exacerbation and cytokine storms. As a result, for covid-19 these inflammation-inhibiting drugs are effective. Many Bhasma preparations have anti-inflammation properties. Rajata Bhasma, Swarna Bhasma, Yashada Bhasma, and Tamra Bhasma are such anti-inflammatories. Tamra Bhasma (copper NPs) has been shown to possess significant anti-inflammation properties. This is accomplished by lowering interleukin and TNF- production (Bafna and Patil 2018). Some metal NPs kill viruses by destroying their envelopes or preventing them from replicating. By degrading the capsid protein, Tamra Bhasma expedites virucidal effect against Covid-19. The Rasayana (immunomodulator) effect of Ayurvedic Bhasma preparations may be used as a vaccine adjuvant. In order to induce a quicker and stronger immune response, immunomodulators in Ayurveda can be used in conjunction with the vaccines of covid-19 (Sarkar and Das Mukhopadhyay 2021). Due to their antimicrobial properties, copper, silver, and zinc NPs are thought to be very effective in fighting covid-19 and preventing contamination and contagion. The

antiviral effects of copper salt nanoparticles have been emphasised. Rajata Bhasma, Tamra Bhasma, Yashada Bhasma, and other Bhasmas with copper-containing drugs, such as Makshika Bhasma (chalcopyrite nanoparticles), are also effective against covid-19 (Sarkar and Das Mukhopadhyay 2021). Although metal NPs have a lot of potential to influence covid-19 therapeutic targets, research on their use to combat covid-19 is only sporadic. Because of their antiviral, immunomodulatory, anti-inflammatory, and adjuvant properties, Ayurvedic metal NPs, particularly Tamra Bhasma, Swarna Bhasma, Vashada Bhasma, and Rajata Bhasma, can be used as novel antiviral agents against the covid-19 virus (Sarkar and Das Mukhopadhyay 2021).

By interacting with the envelop glycoprotein gp120, HIV replication can also be inhibited by silver-copper alloy (Elechiguerra et al. 2005). Copper nanoparticle interactions with *E. coli* produce cavities in the bacterial cell walls, based on scanning electron microscopy studies. When the NPs have high surface-to-volume ratio its antibacterial behaviour is more effective (Raffi et al. 2010). Metal NPs have high surface free energy, which causes them to clump together (Raffi et al. 2010). Copper NPs have antibacterial properties owing to their ability to adhere to bacteria due to their opposite electrical charges, which causes a reduction reaction on the bacterial cell wall (Argueta-Figueroa et al. 2014). The number of colonies found on solid nutrient agar plates was dependent on the concentration of copper NPs, the number of colony forming units CFUs decreased significantly as the concentration of copper NPs increased. In samples containing nanosized copper particles at 60 g CuO/mL and more, virtually no bacterial colonies grew. Only a pause in the lag phase was observed at lower concentrations of NPs, indicating that copper acted as a micronutrient for bacteria, while bacterial growth stopped at higher concentrations. In samples which contain 100 g CuO/mL nanosized copper particles, the approximate  $\text{Cu}^{2+}$  ion concentration emitted from the NPs in liquid medium was the highest. These findings support the hypothesis that a sufficient concentration of copper ions in liquid medium inhibits *E. coli* development (Raffi et al. 2010). Copper ions can induce intracellular ROS formation by interacting with plasma membranes, cellular nucleic acids or proteins making it toxic for most of the organisms, including humans,

at higher concentrations. Based on these understandings metallic and nanoparticle forms of copper, such as tubes, sheet, and oxide NPs, are used as antimicrobial and antiviral agents. Metallic copper used in aqueous solutions allows the controlled release of copper ions (Shionoiri et al. 2012).

In a number of commercial and residential settings, the leading cause of acute gastroenteritis is human norovirus. Stopping norovirus outbreaks requires techniques for quick detection, treatment and disinfection of virus. Inactivation of virus through NPs is a more appealing substitute for other chemical and physical approaches. The mechanism of inactivation of noroviruses using copper involves RNA degradation as well as capsid destruction (Broglie et al. 2015). Since copper NPs have a strong affinity towards sulphur and phosphorous-containing compounds including DNA, when they penetrate within the bacteria, they can inflict harm by communicating with them.  $\text{Cu}^{2+}$  ions can form electrostatic bonds with the plasma membranes and then by the opening or closing of membrane channels they will penetrate the cell membrane.  $\text{Cu}^{2+}$  ions invade cells and form tight bonds with intracellular amino acids and proteases, causing cell death and denaturation of proteins. The NPs which accumulate on the envelope proteins are thought to destabilise the outer cell wall, which causes a potential in the plasma membrane to collapse and the level of intracellular ATP to be depleted, resulting in cell death (Raffi et al. 2010). Copper has the capability to disrupt functioning of cells in a variety of ways, as multiple processes acting in concert can reduce the potential of microorganisms to develop resistance against copper. The mechanisms investigated shed light on the antimicrobial action of copper NPs. Copper NPs have full cytotoxicity against *E. coli* at high concentrations. These NPs bind to the cell wall of bacteria and pass through the membrane. The bacterial cell wall is thus destroyed by copper ions, which causes it to thicken and coarsen and then the cytoplasm will be weakened and disappears, resulting in cell death (Raffi et al. 2010).  $\text{Cu}^{2+}$  solute from NPs can enter the cells by transport and ion/voltage-gated channels, or NPs can disperse across the cell membrane or virus capsid. While NPs can produce ROS in cells by interacting with redox active proteins or oxidative organelles,  $\text{Cu}^{2+}$  which are released by NPs can also generate ROS through a variety of chemical reactions, and the ROS can break the strands of DNA

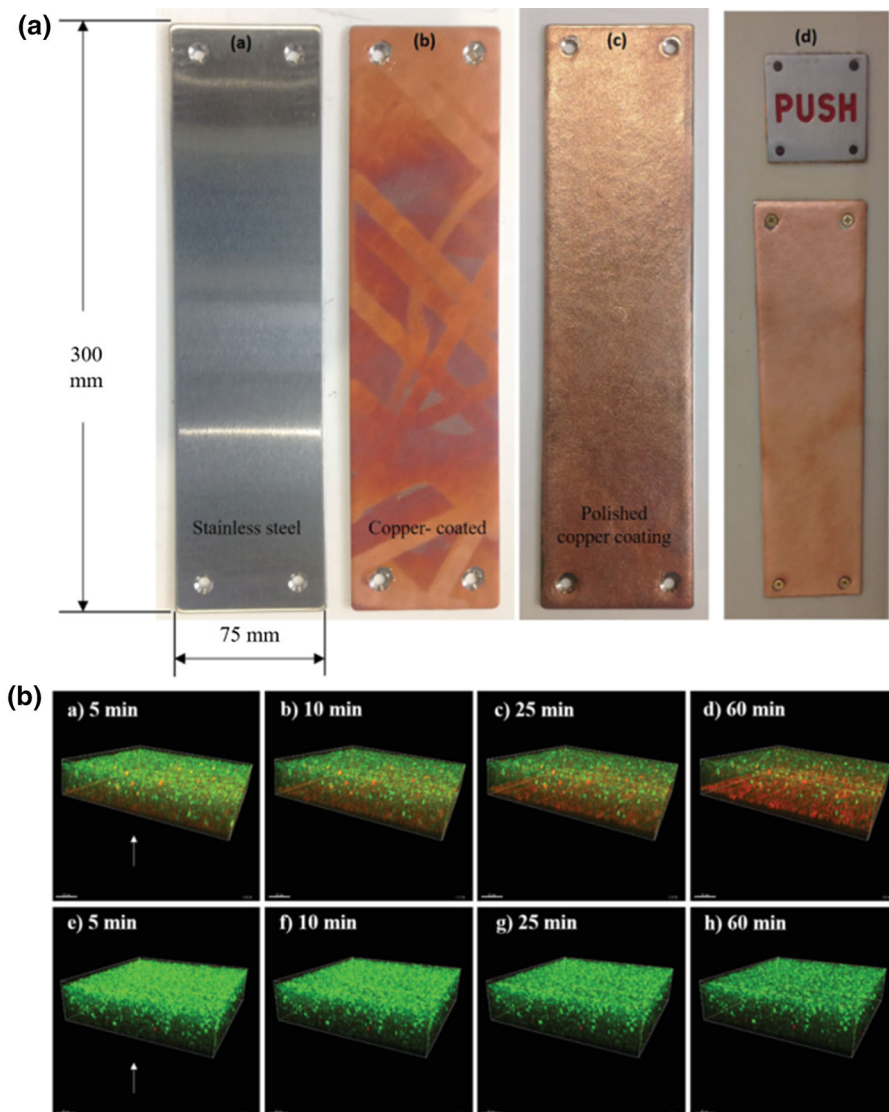
and change the gene expression.  $\text{Cu}^{2+}$  can also form complexes with biomolecules or displace metal ions in specific metalloproteins, causing protein degradation and ultimately cell inactivation. (Broglie et al. 2015). Copper NPs have been shown to be efficient against a wide range of pathogenic bacteria, algae, fungus, and viruses in biostudies. It is also stated that it possesses anti-parasitic and anti-cancer qualities (Ingle et al. 2014).

### Copper based coating technologies

Replacing the bulk components to copper-based materials may not be a viable solution in terms of feasibility as well as economic constraints. Coating with copper-based materials, represents an efficacious strategy to increase copper touching surfaces with antiviral properties. Cold spray technique is an effective method to deposit copper on surfaces, which is compatible with a wide range of substrate materials. An improved viricidal activity against covid-19 virus was exhibited by cold-sprayed copper coatings on stainless steel push plates in a short duration of 7 min (Hutasoit et al. 2020). Cold-sprayed copper coatings were found to possess a thickness of about 0.7 mm (Fig. 7a), which displayed 96% and 99.2% inactivation of Covid-19 after 2 h and 5 h, respectively. This technique has been described as a ‘quick and easy fix’ method of copper coating in a shorter duration to reduce the spread of Covid-19 virus. Apart from cold-spraying, thermal spray technique based on wire-arc spraying of copper onto stainless steel substrate has been reported (Kocaman and Keles 2019). Against ATCC 29,213 *Staphylococcus aureus*, clinically isolated *Pseudomonas aeruginosa*, *E. coli*, Vancomycin-resistant Enterococcus, and Methicillin-resistant *Staphylococcus aureus*, effective microbiological eradication was achieved in a shorter time. Strong killing effect has been attributed to copper ion attack, characteristic rough surfaces, pores and internal stresses. Similarly, twin wire arc type thermal sprayed CuNiZn based copper alloy coatings in hospitals in Canada and Peru were evaluated under real hospital settings (Mostaghimi et al. 2021). The coatings were applied on chair arms, cabinet handles, charting tables and push plates/handles for doors. These thermal sprayed copper coatings are found to be long-lasting, durable and highly antibacterial surfaces with low maintenance.

Effective antimicrobial activity under dry conditions was displayed by prospective electroplated copper–silver coatings deposited on stainless steel substrates as shown in Fig. 7b (Ciacotich et al. 2019). Improved bacterial resistance has been explained to be arising from (a) bacterial cell oxidation due to galvanic coupling induced redox reaction, (b) copper ion release and (c) localised rise in pH. In addition, the developed surfaces displayed biofilm eradication of gram positive bacteria within a shorter period of time as compared to slow removal of gram negative bacterial biofilms.

The majority of coatings produced and commercialised to date are antibacterial, however there have been only less reports on antiviral coatings. Therefore, to battle the increase of viral pandemics and virus-related mortality risks, it is extremely desirable to find appropriate antiviral and viricidal elements to produce hygiene implements, personal protective equipment (PPE). (Huang et al. 2020). Antiviral coatings can be divided into three major groups depending on material type used at the contaminated surface. They are metal ions/metal oxides, antiviral polymers, and functional nanomaterials. Covid-19 can be inactivated by Cytac-Coat, which is the primary antimicrobial covering made with biocompatible organic components. For controlling the spread of covid-19 virus, it can be applied in face masks since it doesn’t depend on toxic metal oxides or metal ions (Odeberg et al. 2018). Fluidic compounds with good antiviral effectiveness are being developed as supportive coatings. In substances like toys, medical devices, notes, and cards that can potentially carry viruses are designed to cover with fluidic composition. Therefore, these fluidic compositions could avoid the contamination due to the presence of virus. For antiviral coatings material with strong water repellence qualities is preferred. Rossett et al. (Rossett 2014). discussed a fluidic composition containing single antiviral viricide, such as laurel essential oil or soya bean oil, lauric acid, and essential oils. Because of the viricide’s capabilities, the surface seems transparent, with an effective coating (Rossett 2014). A powdered substrate solution and an organic acid were proposed by Fox et al. (Fox et al. 2011) as a viable antiviral composition. For the elimination of rhino and rota viruses, this solid combination could be applied directly to the substrate. Composition plays a key role in the destruction of non-enveloped and enveloped influenza viruses, as well as



**Fig. 7** **a** Cold-sprayed copper coated stainless steel push plates installed on doors. Reprinted from (Hutasoit et al. 2020) with permission from Elsevier. **b** Increased bactericidal activity as evidenced by the presence of more dead cells (red colour, *a–d*)

on copper–silver alloy coating compared to uncoated stainless steel surfaces with predominant live cells (green colour, *e–h*). Reprinted from (Ciacotich et al. 2019) with permission from Wiley. (Color figure online)

the maintenance of antiviral activity by forming a thin coating of organic acid on the surface. These antiviral compositions offer some highly effective remedies against a wide range of viruses, as well as the ability to generate them at a cheaper cost (Fox et al. 2011). Conductive nanocoating of materials/metals onto surfaces (photothermally or electrically) through robust and sterile methods such as non-thermal plasma process could be used in the future for delivering nanomaterials-driven anti-infective surfaces for long-

term/reusable applications and for sterilising surfaces (Pemmada et al. 2020). Antiviral coating materials made of nanomaterials with a significant light heat impact, such as those with LSPR and those with significant light absorption capabilities, can form localised hot-spots under light stimulation and destroy viruses or inactivate the proteins of the spikes. There are several active small compounds that can attach to virus spike proteins and inactivate them, which can be used to build future antiviral coatings. The covid

pandemic made us aware of the fact that how much less we know about the world we live in and at the same time, it generated humongous knowledge and rapid rise in technology especially in the field of pharmaceutical technology and biotechnology. Now it is high time for the vaccine technology to evolve and adapt to newer technologies with higher efficacy and rapid production (Sun and Ostrikov 2020).

In spite of its excellent antiviral properties, copper-based materials have some limitations which need to be taken into account for effective medical applications. Copper is essential for humans in moderate levels. But excess of copper and deficiency of copper affects health. Since deficiency and excess of copper can have negative health effects, assessing copper specifications and upper safe limits for intake is difficult. Since copper is expensive and harder to clean without causing corrosion, its widespread use for medical application is limited. On exposure of air, copper undergoes rapid oxidation which in turn limits its antimicrobial use in aerobic condition.

## Conclusion

Bacteria, viruses, and other disease-causing microorganisms are more likely to be found in public places like airports, shopping centres, and hospitals. Since the covid-19 virus that is causing the pandemic is so contagious, it is critical to keep the virus from spreading further. The influence of copper can be summarized as follows,

1. On copper surfaces, the covid-19 virus is active for less than 4 h, compared to plastic and stainless steel on which the virus was present for more than three days.
2. Therefore, if the contact surfaces are made of copper, the spread of the disease would be minimized. In addition, copper is preferred for doorknobs, push plates, handles, stair railings, restroom faucets, and other applications. All of these public surfaces are more prone to spread disease-causing microbes to hands, resulting in infection.
3. Copper has inherent antimicrobial properties. When cleaned thoroughly and on a regular basis, infectious pathogens can be effectively inactivated on regularly touched surfaces made of uncoated copper alloy materials.
4. The exposure of copper to covid-19 has been reported to inactivate viral genomes and showed an irreversible impact on virus morphology, including envelope disintegration and surface spike dispersal.
5. Since corona viruses are structurally similar, copper alloy's anti-coronavirus activity is likely to be effective to all coronavirus strains.

Of course, hand washing, good hygiene, and social distancing remain the most successful ways to fight covid-19 or any such viruses. However, strategic copper usage will complement these steps, allowing the physical environment to effectively combat harmful bacteria and viruses.

## Declarations

**Conflict of interest** On behalf of all authors, the corresponding author states that there is no conflict of interest.

**Consent for publication** All the authors in this investigation gives the permission to the publisher to publish the work if accepted.

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