



# Nanostructured coatings based on metallic nanoparticles as viral entry inhibitor to combat COVID-19

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## ABSTRACT

The rapid transmission of contagious viruses responsible for global pandemic and various extraordinary risk to precious human life including death. For instance, the current ongoing worldwide COVID-19 pandemic caused by novel coronavirus (SARS-CoV-2) is a communicable disease which is transmitted via touching the contaminated surfaces and then nosocomial route. In absence of effective vaccines and therapies, antiviral coatings are essential in order to prevent or slowdown rapid transmission of viruses. In this prospective, sustainable nanotechnology and material engineering have provided substantial contribution in development of engineered nanomaterial based antiviral coated surfaces to the humanity. In the recent past, nanomaterials based on silver (Ag), titanium oxide (TiO<sub>2</sub>), copper sulfide (CuS) and copper oxide (CuO) have been modified in the form of engineered nanomaterials with effective antiviral efficacy against SARS-CoV-2. In this review, various recent fundamental aspects for fabrication of metallic nanoparticles (Ag, Ti, Cu etc.) based coated surfaces on various substrates and their antiviral efficacy to inhibit viral transmission of SARS-CoV-2 are discussed along with their respective conceptual mechanisms. The antiviral mechanism based on chemistry of engineered nanomaterials is the key outcome of this review that would be useful for future research in designing and development of more advance antiviral materials and coated surfaces in order to control of future epidemics.

## 1. Introduction

In general, a single or double stranded (DNA or RNA) based genetic material and protein-based capsid with an outer lipid envelope are main constituent of the viruses [1,2]. Viruses are considered as submicroscopic entities because of their multiplication ability only inside the cell of micro and macro-organism. In addition, they are one of the air-transmitted pathogens and responsible for various human diseases from common cold to the severe respiratory illnesses in crowded and indoor places either via directly human contact (blood transfusion, sneezing, coughing etc.) or through infected vectors such as animals and insects [2,3]. For instance, the current ongoing pandemic of Coronavirus disease 2019 (COVID-19) caused by a virus of Coronaviridae family named as severe acute respiratory syndrome coronavirus 2 (SARSCoV-2), which is a contagious disease [4]. Initially, this disease was reported in Wuhan city of central China in December 2019. Within a short period of time spread to >200 countries including India and declared as pandemic by the World Health Organization on 11th March 2020 [4,5]. Because of the contagious nature and rapid spreadability, COVID-19 becomes a global health crisis and leads to millions of death

throughout the globe [1]. The main reason of COVID-19 transmission is the persistent nature of the SARSCoV-2 on the various surfaces (cellulose, metallic and polymeric substances) from hours to days which quickly fall from virus-laden droplets of cough, sneeze and exhale from infected persons [6–8]. The contact of such virus contaminated surfaces through the respiratory system (by touching the mouth, nose and eyes) might be able to infect other healthy persons [9,10]. Thus, the lack of effective approach to prevent the viral transmission and their stability on various surfaces from hours to day remains a primary challenge in the fight against diseases spread by the contagious SARSCoV-2. Therefore, in order to control the ongoing and in future contagious viral disease, economic and effective antiviral agents are highly needful.

In the recent past years, nano-materials with particle size in the range of 1–100 nm are considered as effective alternative for environmental remediation application [11–14] [15,16] as well as against various diseases caused by harmful viruses and bacteria because of their high surface area to volume ratio, small sizes, modifiable surfaces and excellent biological activities [17]. The excellent virucidal efficacy of metallic nanoparticles such as titanium (Ti), zinc (Zn), silver (Ag), copper (Cu) etc. make them highly useful as a coating materials to tackle

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the severe viruses infections [17–22]. Among the various nano-materials, the use of Cu nanoparticles in order to inactivate or blocking the entry of viruses has been reported remarkably because of its easy modification ability in desired properties. Cu is one of the highly essential elements for a wide range of essential biological functions. According to the result of National Health and Nutrition Examination Survey (NHANES III, 2003) in the USA, the daily intake of Cu in human body was recommended as 1.54–1.7 mg/day for men and 1.13–1.18 mg/day for women (varied with the age) for the proper biological functions [19]. Moreover, Cu also needful for the human immune system and plays an important role in the maintenance of neutrophils, white blood cells, B cells, natural killer cells and T helper cells [23]. These cells are highly needful for the production of specific antibodies, to enhance cell-mediated immunity as well as also to killing the infectious microbes [19,24]. In addition, it has been also reported that Cu can kill variety of enveloped and non-enveloped viruses with single or double stranded DNA and RNA genetic materials such as human immunodeficiency virus type 1(HIV-1), poliovirus, and bronchitis virus including SARSCoV-2. Because of this excellent ability, researchers have developed various antiviral solutions using this nanoparticle and examined their efficacy to prevent the transmission of contagious viral infections in humans since beginning of COVID-19.

In this review, the recent advances related to the application of Ti, Ag, Zn, Cu nanoparticles and its modifications for developing antiviral surfaces on different substrate using different approaches have been highlighted. Moreover, this review specially focused on the use of Cu nanoparticles (CuS, CuO, and Cu<sub>2</sub>O) with different methodologies to develop antiviral coatings. Also discussed the mechanism of action based on the platform of the Cu nanoparticles in order to control the emerging transmission of viral infections including COVID-19.

## 2. Metal and metal oxide nanoparticles based antiviral surfaces and coatings

The metal or metal-oxide based nanoparticles have been widely studied for antiviral surface coatings because of their unique physico-chemical properties along with high specific surface area to volume ratio [25,26]. Metallic nanoparticles based coated surfaces could attack viruses through various pathways including (i) generation of reactive oxidative radicals and controlled release of disinfectant metal ions to

inactivate viruses (via lipid envelope damage, protein disruption, oxidative stress etc.), (ii) high binding affinity with protein of virus surfaces and cleavage of disulfide bonds, (iii) photothermal effect to converge in a particular source of light [25–29]. Several methods have been reported for fabrication of metallic nanoparticle based coating on the surface of various substrates. Some of the commonly used methods to apply metallic nanoparticles based surface coatings are summarized in Table 1 along with the brief description about advantages and disadvantages of each approaches [22,30–32]. Among these methods, spray-coating and dip coating have been used extensively for nanoparticle coatings because of their simplicity in application and easy to handle without requirement of any special equipment [22]. Moreover, metallic nanoparticles can be functionalized with specific functional groups or antibodies before their utilization in coating solution in order to enhance viral binding ability and higher potency to inactivate viruses. Recently developed metallic nanoparticles (Ag, Ti, Zn, Fe, and Cu) based coated surfaces along with their antiviral properties are summarized in the subsequent sections.

### 2.1. Silver oxide nanoparticles

Ag nanoparticle (Ag NPs) based coatings have been explored extensively for their antiviral potential on the surface of various types of substrates [26,37,38]. Ag NPs show efficient antiviral potential owing to their higher surface area and continuous silver ions releasing ability from coated surfaces [39]. The interaction of silver ions with viruses resulting in inactivation of various cellular factors which are essential for viral replication [38,39] [Fig. 1].

Moreover, many recent works evaluated the influence of physicochemical properties of Ag NPs on their antiviral potential in order to prevent the contagious viral infections including SARS-CoV-2. For instance, Jeremiah et al. [37] evaluated antiviral properties of Ag NPs with different sizes (1 to 1000 nm) and concentrations (1 to 10 ppm) against SARS-CoV-2 through virus pre-treatment assay approach. In the present work, initially, virus was treated with Ag NPs and the resultant mixture of virus-Ag NPs was added to the cell lines VeroE6/TMPRSS2 (non-human origin) and Calu-3 (human lung epithelial cell). After 96 h, viral copies (viral load) in supernatant was examined using real time reverse transcriptase quantitative polymerase chain reaction (RT-qPCR). The authors observed steep fall in the viral load to negligible levels and

**Table 1**

Commonly applicable methods for fabrication of metallic nanoparticle based coating on the surface of various substrates.

Coatings methods	Process	Advantages	Disadvantages	References
Dip-coating	Dip coating method involves the use of coating solution containing functionalized nanoparticles along with chemically active components. Selected substrates for coating are fully immersed in coating solution for a specific period of time, after that lifted out and subjected to dry either via thermally cured or in air at a particular temperature.	<ul style="list-style-type: none"> <li>• Easy to applicable</li> <li>• Scalable</li> <li>• Reduced waste generation</li> <li>• Applicable for planar as well as 3D materials.</li> </ul>	<ul style="list-style-type: none"> <li>• Requirement of high smooth surfaces of selected substrates.</li> <li>• Issues in controlling coating thickness at <math>\mu\text{m}</math> to nm scale.</li> </ul>	[22,33–35]
Spray coating	In this method, coating material along with nanoparticles is sprayed onto surface of the selected substrate at a particular rate of solvent evaporation.	<ul style="list-style-type: none"> <li>• Easy operation</li> <li>• Scalable process</li> <li>• Respraying option offer repairing</li> <li>• No any requirement of specific substrate</li> </ul>	<ul style="list-style-type: none"> <li>• Optimization of evaporation rate of solvents.</li> </ul>	[22,30,33]
Spin-coating	In this process, coating procedure generally completed in four successive stages: (i) applying coating solution on the surface of target substrate, (ii) spin up at a particular speed for a certain time, (iii) spin off, (iv) evaporation of residual solvents and drying.	<ul style="list-style-type: none"> <li>• Fine coating can be prepared with uniform and thin layer.</li> <li>• Thickness of coating can be controlled according to desire application.</li> </ul>	<ul style="list-style-type: none"> <li>• Difficult to operate on substrate of larger size.</li> <li>• Possibility of wastes of coating materials during high speed of spinning process.</li> </ul>	[22,30,33]
Vapor deposition method	This method involves multidirectional deposition of coating materials on the surface of heated substrate.	<ul style="list-style-type: none"> <li>• Facile, rapid and easy applicable</li> <li>• Hierarchical structure can be prepared</li> </ul>	<ul style="list-style-type: none"> <li>• Commonly applicable to selective substrates such as metallic or ceramic composition</li> <li>• Unsuitable for cellulose other soft materials</li> <li>• Requirement of specific heat treatment at high temperature</li> </ul>	[36]

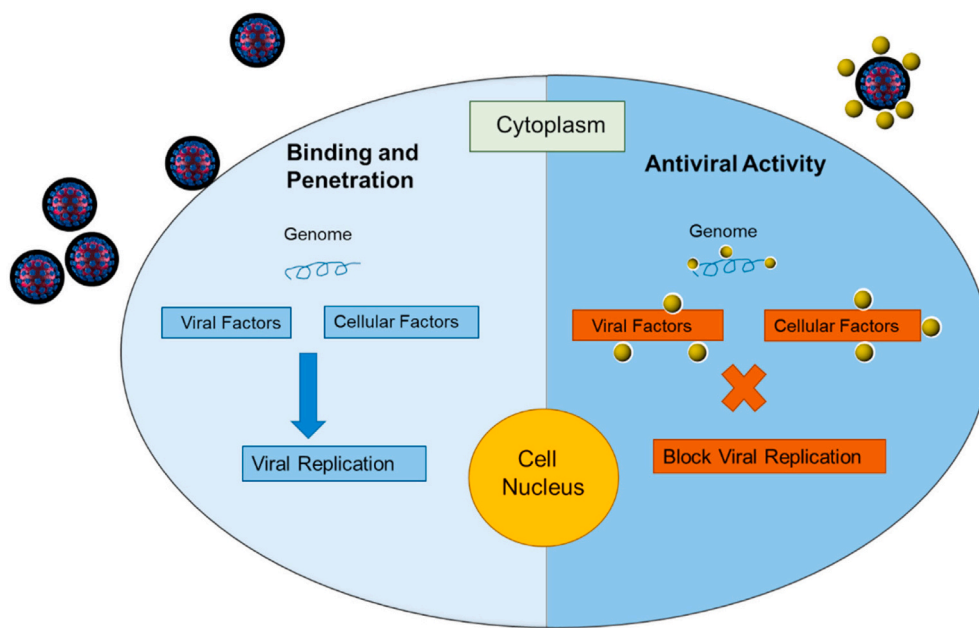
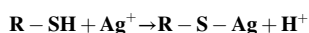
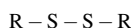


Fig. 1. Schematic representation of antiviral mechanism of silver nanoparticles. Reproduced with permission from ref. [38], Copyright 2021, Elsevier.

excellent reduction in cell death by the use of Ag NPs around 10 nm diameters at concentration in the range of 1 to 10 ppm. The major reason behind the excellent antiviral efficacy of Ag NPs is the cleavage of disulfide bridges (according to following reactions) of virus spike proteins and cellular dysfunction which leads to inhibition in viral infectivity newly generated virus [40–44]. Here disulfide bond and cysteine residues are represented as R – S – S – R and R – SH.



Balagna et al. [45] reported coating (>200 nm) of silver nanocluster/silica based composite on facial masks through co-sputtering process in pure argon atmosphere and evaluated its antiviral behavior towards Coronavirus SARS-CoV-2. In this study, authors isolated 100 µl of 50 TCID<sub>50</sub>/ml SARS-CoV-2 viral strain from a symptomatic patient and added to the pieces (1 cm<sup>2</sup>) coated and uncoated facial masks. Thereafter, both types of treated facial mask pieces were placed in petri dish for incubation at room temperature. The formation of cytopathic effect and staining of viable cells were used as parameter in order to assess the infectivity of the virus.

It was observed that coated facial masks completely reduced cytopathic effect, while higher infectivity was observed in case of uncoated mask. Additionally, it was also reported that this coating can be applied on the surface of various types of substrates such as glasses, ceramic, metals, polymers etc. From the obtained results, authors concluded that silver nanocluster/silica composite coated facial masks can be effective contribution for safety in crowded areas from viral infection.

Tremiliosi et al. [21] also reported Ag NPs (average size ~23.51 ± 5.18 nm) coatings on polycotton (67% polyester and 33% cotton) fabrics using pad-dry-cure method. In this method, a piece of polycotton fabric (30 × 30 cm) was immersed in colloidal solution of Ag NPs along with organic polymers (acrylic based binder) for a specific period of time. Thereafter, treated polycotton fabric was dried (at 80 °C for 3 min), annealed (at 170 °C for 3 min), washing with deionized water and finally dried in an ventilated oven at 80 °C for 3 min. The antiviral activity of the Ag NPs coated polycotton fabric was examined via inoculation of SARS-CoV-2 into three separate liquid media containing coated fabric,

uncoated fabric and without any fabric. After the incubation period (certain different period of time) the genetic material of virus (viral load) was examined using real-time quantitative PCR. Authors observed excellent inhibition rate (>80%) of Ag NPs coated polycotton fabric with respect to SARS-CoV-2. The authors postulated the major reasons behind the high anti-SARS-CoV-2 activity are the (i) generation of reactive oxygen species from Ag NPs and its interaction with DNA, (ii) binding ability of Ag NPs with the sulfur residues of glycoproteins on virus's surface and responsible for inhibition of viral replication.

## 2.2. Titanium dioxide nanoparticles

Titanium dioxide (TiO<sub>2</sub>) nanoparticle is known for its photocatalytic application with a wide band gap of 3.2 eV [46–48]. The excitation of electron takes place from electron band to conduction band when TiO<sub>2</sub> exposed to UV light having energy equal to or higher than its band gap [48]. This phenomenon led to formation of holes and electron which are capable to produce reactive oxygen species (ROS) with unpaired electrons by the interaction with water (H<sub>2</sub>O) molecules or ambient oxygen (O<sub>2</sub>) or moisture [26]. These generated ROS on the surface of TiO<sub>2</sub> are not only useful in degradation of organic matter during water treatment application but also for the disinfection of bacteria/microbes [46,49]. The potential of TiO<sub>2</sub> nanoparticles has been extended to antiviral activity (disinfection of viruses including SARS-CoV-2) by the coatings on the surface of various substrates. For instance, Khaiboullina et al. [29] studied, virucidal efficacy of TiO<sub>2</sub> nanoparticles induced by the UV radiation towards deactivation of SAR-CoV-2. In the present work, TiO<sub>2</sub> nanoparticles were coated on glass coverslip. An aliquot (100 µL, 2.1 × 10<sup>5</sup> TCID<sub>50</sub>) SAR-CoV-2 was placed on TiO<sub>2</sub> nanoparticles coated and uncoated coverslips (18 mm diameter, 1017.88 mm<sup>2</sup>) and exposed to a source of UV light (wavelength: 254 nm, 99 V, 30 W, 0.355 A) for various time points. Virus infectivity assays was determined by genomic RNA quantitation using RT-qPCR. Authors observed total inactivation of virus within 5 min of UV light exposure on the surface of TiO<sub>2</sub> nanoparticles coated coverslips. On other hand significant copies of intracellular genomic RNA was observed on the without treated coverslips. Additionally, authors also reported that viral inactivation activity of TiO<sub>2</sub> nanoparticles coated surfaces was maintained even on the virus droplet has been dried. Hence from the above observation, it can be concluded that TiO<sub>2</sub> nanoparticles based coatings can be used for

various substrates in order to inactivation of contagious SAR-CoV-2.

In another study, Hamza et al. [50] synthesized  $\text{TiO}_2$  nanotubes by the sol-gel method in basic medium, followed by the hydrothermal treatment at  $150^\circ\text{C}$  for 12 h. The antiviral efficacy of the synthesized  $\text{TiO}_2$  nanotubes was examined respect to SAR-CoV-2 and determined Inhibitory Concentration 50% ( $\text{IC}_{50}$ ). Authors observed that synthesized  $\text{TiO}_2$  nanotubes exhibited excellent anti-SAR-CoV-2 activity even at very low concentrations ( $\text{IC}_{50} = 568.6 \text{ ng mL}^{-1}$ ) along with weak cytotoxic effect. Authors postulated that major reason behind this excellent antiviral activity is the ability of  $\text{TiO}_2$  nanotubes to release a large quantity of  $\text{Ti}^{+2}$  ions and variety of free radicals (reactive oxygen species). These free radical and metallic cations can damage protein and lipids including nucleic acid strains. Thus authors concluded that  $\text{TiO}_2$  nanotubes based coated surface can be used for inactivation of SAR-CoV-2 on various substrates.

### 2.3. Zinc oxide nanoparticles

Zinc is essential metal in biological systems because of its utility as coenzyme, body's immunity booster and as signaling molecule in regulation of inflammatory responses [51–53]. In addition to this zinc oxide (ZnO) nanoparticles has been considered as potential antibacterial metallic nanoparticles including viruses [54]. ZnO can also act as photocatalyst in presence of artificial UV or sunlight and water because of its similarity in band gap to  $\text{TiO}_2$  nanoparticles [55,56]. During the exposure with artificial UV or sunlight reactive oxygen species are generated from the surface of ZnO nanoparticles [55–57]. These reactive oxygen species (hydrogen peroxide, superoxide, hydroxyl radicals etc.) can damage the biological membranes of bacteria or viruses [57,58]. It has been reported that nanoparticle form of ZnO is safe for human contact, as it is consumed as supplement in limited level and also utilized in sunscreens [59]. Because of these specific features, ZnO nanoparticles can be used as coating materials for the inactivation of contagious viruses.

### 2.4. Iron oxide nanoparticles

Iron oxide (IO) ( $\text{Fe}_2\text{O}_3$  or  $\text{Fe}_3\text{O}_4$ ) nanoparticles have drawn prominence in variety of applications including biomedicine, water treatment, electronics and agriculture because of their high biocompatibility, electrical, magnetic and optical properties [60–62]. In addition to these applications, antiviral efficacy of the IO nanoparticles is also reported via various mechanisms including binding ability to virus surface proteins and damaging of viral envelope, lipid peroxidation and ROS generation [26]. In a theoretical study, Abo-zeid et al. [63] evaluated binding affinity of SARS-CoV-2 spike protein to  $\text{Fe}_3\text{O}_4$  (magnetite) and  $\text{Fe}_2\text{O}_3$  (hematite) nanoparticles. Authors reported that IO nanoparticles may inhibit the attachment of SARS-CoV-2 spike protein to the host cell. In addition authors also proposed that reactive oxygen species on the surface of IO nanoparticles can inactivate the virus by oxidative damage the viral lipid envelope.

## 3. Copper-based antiviral surfaces and coatings

In the recent past, Cu-based nanoparticles such as copper sulfide, cuprous oxide and cupric oxide have been explored extensively for antiviral coatings on various surfaces because of their various favorable characteristic features such highly non-cytotoxic, non-irritating to skin and safe for human contact [64]. Experimental studies provided evidence with respect to antiviral efficacy of Cu coated surfaces against various viruses including SAR-CoV-2.

For instance, Hewawaduge et al. [65] fabricated self-sterilizing antiviral three layer mask design based on nylon fiber along with the incorporation (coating as well as impregnation) of copper sulfide and evaluated the antiviral efficacy of the designed mask against SAR-CoV-2. In this study, copper sulphide was incorporated in only outer and

middle layer and its percentage (w/w) was varied in the mask layers. Authors impregnated total of 17.6% CuS (w/w) in middle entrapment area and 4.4% CuS (w/w) (2.2% CuS coated & 2.2% CuS impregnated) in outer layer. Thus total load of copper sulfide in the three layer nylon mask was approximately 22 g per 100 g of total mask weight. The inner layer was designed in specific way to provide comfort and safety for users without incorporation of copper sulfide. The authors examined consistency of fiber thickness after coating and uniform distribution of particle by the use of scanning electron microscopy (SEM). The rough and smooth surface of CuS coated and CuS impregnated were clearly observed in the analyses of SEM images [Fig. 2a].

Authors evaluated the antiviral properties of solid state  $\text{CuSO}_4$ , copper sulfide and copper sulfide incorporated masks of nylon fiber against SARS-CoV-2 by their interactions with a known viral titer (0.1 MOI) for 30 min, 1 h and 2 h of variable durations. Viral inactivation ability was examined by the viral copy number, cytopathology and fluorescence. They observed that the generated  $\text{Cu}^{2+}$  did not show any appreciable viral inactivation ability even after increment of their molar concentration as well as contact (incubation) time. However, in the copper sulfide coated mask, authors observed excellent antiviral efficacy (completely blockage the passing of virus containing droplet) within 30 min exposure and considered as ideal remedy to prevent the SARS-CoV-2 transmission. The schematic representation of three layered nylon mask architecture along with the incorporation of copper sulfide and virus capture mechanism are shown in Fig. 2b.

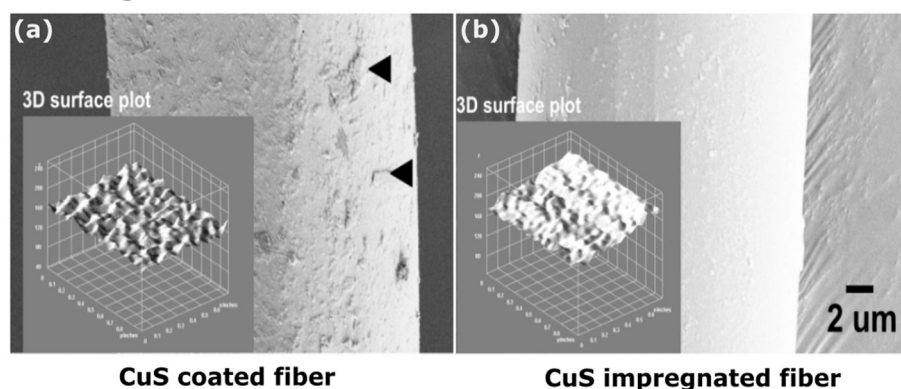
Authors reported that the major reason behind excellent antiviral efficacy coated mask is the potential involvement of sulfide ions ( $\text{S}^{2-}$ ) along with the combination of generated reactive oxygen species due to increased stress of copper. Thus, on the basis of experimental observation authors concluded that the developed self-sterilizing antiviral masks could be advantageous in order to save precious human lives in this ongoing COVID-19 pandemic.

Hosseini et al. [66] fabricated cupric oxide based antiviral coatings with porous and hydrophilic in nature on the glass surface by the dispersion of cuprous oxide suspension in ethanol followed by thermal treatment for 2 h at  $700^\circ\text{C}$ . Because of the thermal treatment, cuprous oxide was converted into cupric oxide and sintered the particles in the form of robust film of approximately  $30 \mu\text{m}$  thick. In this study, the oxidation state of copper was analyzed before and after coating formation by the use X-ray photoelectron spectroscopy. It was observed that hydrophilicity of the developed coating was maintained for at least five months. The authors used Vero E6 cells to prepare virus stock and inactivation ability of the developed cupric oxide coated surface was evaluated against SARS-CoV-2 at  $22\text{--}23^\circ\text{C}$  and 60–70% humidity. Excellent infectivity (99.8% in 30 min) from the CuO film was observed. The authors postulated that attractive charge-charge interaction was the main reason behind the SARS-CoV-2 inactivation efficacy. They explained that the virus spike proteins have net charge of about positive 3.5 at pH 7.4 (spike protein have 1 histidine, 7 anionic and 10 cationic amino acids). As well as virus envelope (E) protein also have net charge positive. However, in the culture medium, surface of cupric oxide have negative zeta potential ( $-17 \text{ mV}$ ). Therefore because of electrostatic force of attraction, SARS-CoV-2 attracted on the cupric oxide coated surface become inactivated. Thus authors concluded the charge-charge interaction mechanism behind the inactivation of SARS-CoV-2.

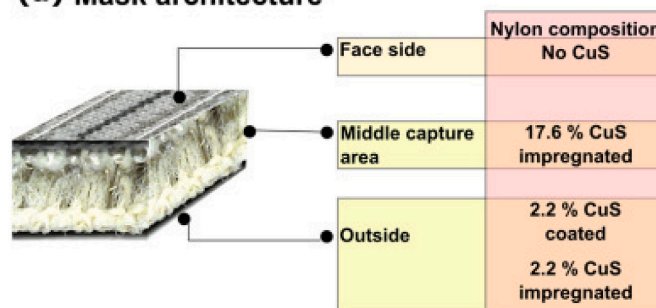
Although, both form of CuO nanoparticles either as Cupric oxide (CuO) OR cuprous oxide ( $\text{Cu}_2\text{O}$ ) are antiviral against both non-enveloped and enveloped, some studies are performed to compared the antiviral efficacy of the CuO nanoparticles in these two oxidation states. For instance, Mazurkow et al. [67] explained the antiviral efficacy of these two forms of CuO nanoparticles on the basis of determination of isoelectric point. They reported 11.0 isoelectric point value (higher positive charge) for  $\text{Cu}_2\text{O}$  and 7.4 for CuO nanoparticles. Authors concluded that  $\text{Cu}_2\text{O}$  with higher positive surface charge will be better in antiviral efficacy due to electrostatic interaction. Similar observations have been reported in other studies with respect different



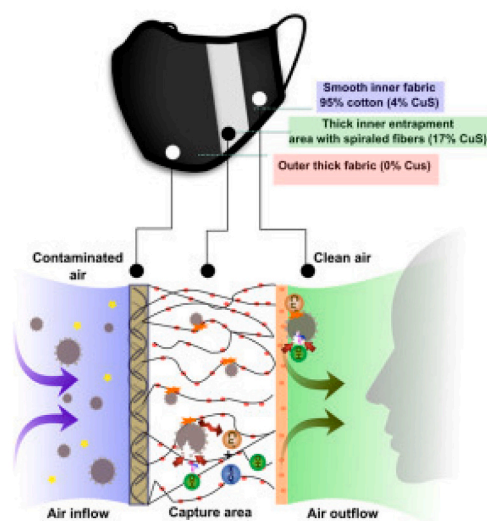
## SEM images of mask fibers



### (a) Mask architecture



### (b) Mask mechanism



**Fig. 2.** a. SEM images mask fibers: (a) coated CuS, (b) impregnated CuS. Fig. 2b. Schematic representation of copper sulfide incorporated nylon fiber based three layered mask and virus capture mechanism (a) The arrangement of mask layers and CuS incorporated fiber composition. (b) Entrapment mechanism of the three-layer mask. Reproduced with permission from ref. [Hewawaduge et al. [65], Copyright 2021, Elsevier. Reproduced with permission from ref. [65], Copyright 2021, Elsevier.

viruses [42,68].

In addition to glass, cotton and nylon fiber, copper nanoparticles based coated was also found effective on metallic surfaces in order to inactivate SARS-CoV-2. For instance, Hotsaot et al. [69] fabricated copper coated touch surfaces on steel parts using cold spray technique. The virus inactivation efficacy of the copper coated surface was examined in vitro by the exposure of 50 mL volume of SARS-CoV-2 containing  $10^{5.5}$  TCID<sub>50</sub> mL<sup>-1</sup> (TCID<sub>50</sub> is a measurement of virus titer and represents the amount of virus that produces an infection in 50% of the cells exposed) to copper surface and left in contact at room temperature for various time interval 1, 10, 30, 120 or 300 min. The authors observed

that synthesized coating of copper significantly reduces the life time of SARS-CoV-2 to below the 5-h. The authors concluded that very short manufacturing time of coatings and high efficiency against viral infection with viral killing property in very short time are highly useful in real life applications.

Furthermore, in order to reduce the virus inactivation time some researchers are tried to utilize the coating of copper nanoparticles along with the combination of some other nanoparticles also on various solid surfaces. For instance, Mosselhy et al. [70] fabricated antiviral coatings of copper-silver (Cu—Ag) nanohybrids via powder coating/wet painting (spray coatings) with thickness of 40 μm. The authors evaluated the

antiviral efficacy of the developed Cu—Ag nanohybrid against SARS-CoV-2 on public places, people's homes, and health care settings (as shown in Fig. 3). The average size of Cu and Ag particles utilized in coatings were  $\sim 26 \pm 2$  nm and  $\sim 212 \pm 16$  nm, respectively. The authors observed that developed coating effectively inhibited SARS-CoV-2 in  $<5$  min. On the basis excellent performance of coated surfaces, they concluded that Cu—Ag nanohybrids based coatings could be employed to prevent the transmission of SARS-CoV-2 in this currently ongoing pandemic. However, the mechanism of virus inhibition efficacy was not discussed in details.

El-Nahhal et al. [71] fabricated copper-coated cotton fabrics by the use of three different types of copper based coating materials such as copper oxide nanoparticles (CuO-NPs), functionalized CuO—Ag nanocomposites and Cu(II)—curcumin complex by the use of dip coating approach along with ultrasonication [Fig. 4]. The antimicrobial activity of the coated fabrics was examined according to the standard quantitative test (AATCC 100, 2004) method.

The particle size of the synthesized CuO—Ag nanocomposite was found 29 nm as examined by the TEM. In addition surface morphology of the coated and uncoated cotton fabrics was analysed by SEM [Fig. 5]. It was observed that CuO coating on have a different morphology as compared to the pristine fabric. Authors reported that the antimicrobial activity CuO—Ag/cotton material was better among all coated surfaces both *E. coli* and *S. aureus*. This behavior might be due to the generation of reactive oxygen species as hydrogen peroxide and electrostatic force of attraction between bacterial cell surface and CuO particles. Thus author concluded that such type of copper and silver nanoparticles based could be applied on medical facilities in order to inhibit the spreading of contagious viruses including SARS-CoV-2.

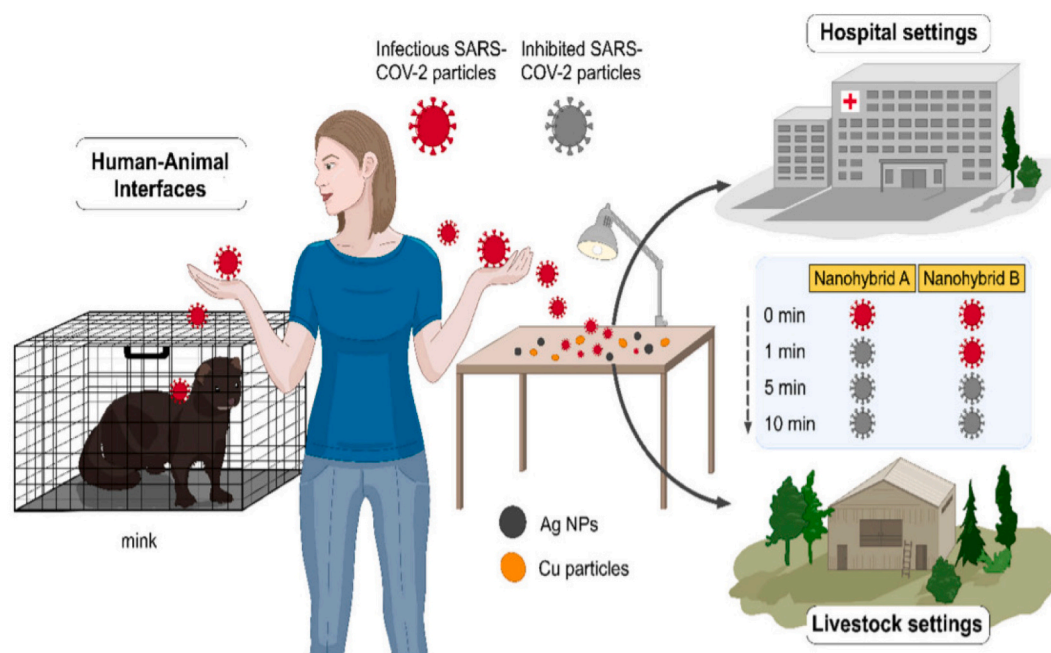
In addition to the single and bi-metallic nanoparticles, some studies have been reported with the use of tri-metallic nanoparticles for inactivation of contagious including SARS-CoV-2 [7,8]. For instance, Robinson et al. [7] reported the utilization of additive manufacturing and surrogate modeling for the development of microporous architecture based on combination copper-tungsten-silver (Cu-W-Ag). In this study, surrogate modeling was highly useful in order to obtain optimal parametric combination which led to obtain microporous system of Cu-W-Ag

with average pore size of 80  $\mu$ m. Interestingly, it was observed that The Cu-W-Ag architecture exhibited 100% viral inactivation with respect to SARS-CoV-2 (enveloped ribonucleic acid viral model). Thus on the basis of observed excellent antiviral behavior authors concluded that Cu-W-Ag architecture is suitable to reduce viral contamination of SARS-CoV-2 on various surfaces.

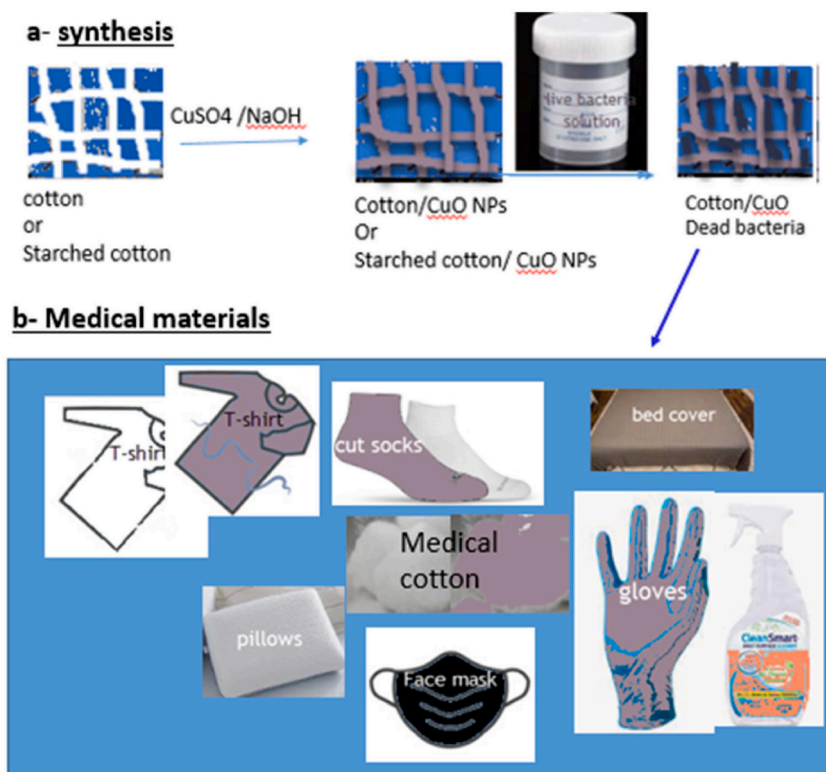
#### 4. Mechanism behind the antiviral efficacy of cu nanoparticles as viral entry inhibitors

The SARS-CoV-2 genome consist of mainly four type of structural protein which are useful for different functional activity such as spike (S) protein (useful for the attachment of virus to host cell), envelope (E) protein (viroporins, phospholipids hydrophobic in nature), membrane (M) protein (shape of the cell can be determine), and nucleocapsid (N) protein (useful for replication cycle in host cell)) (Fig. 6) [4,72]. The presence of copper nanoparticles as a coating material on various surfaces significantly contributed to prevent the transmission of SARS-CoV-2 via direct/indirect disinfection and receptor inactivation pathways.

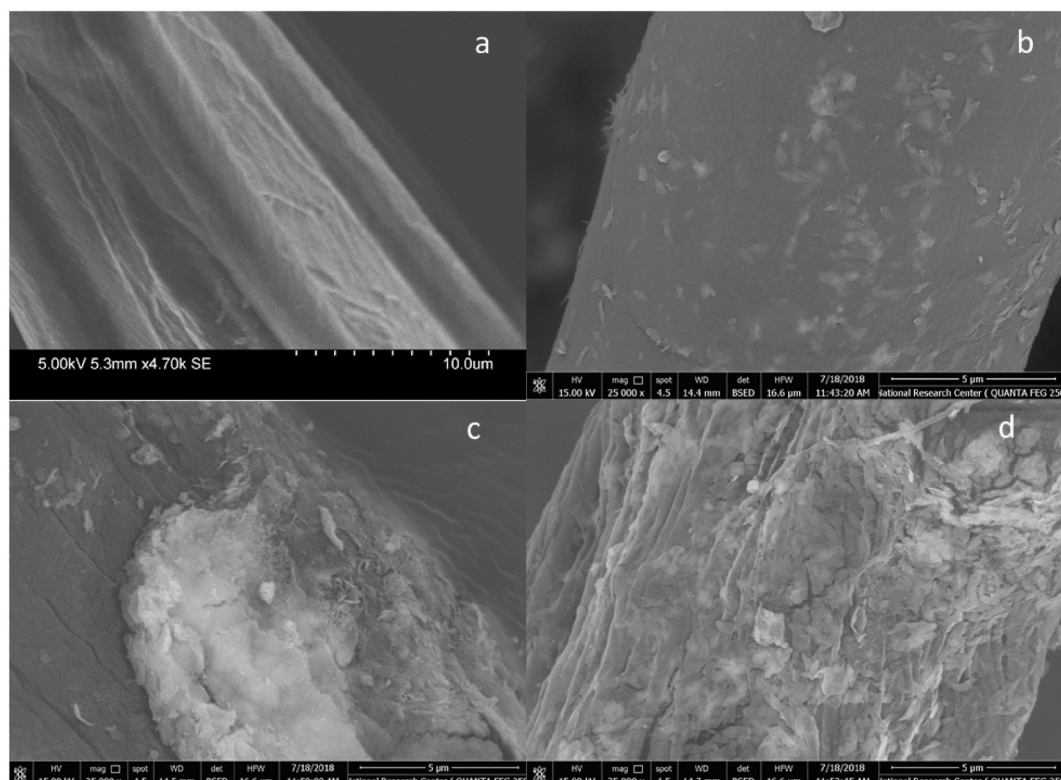
The excitonic effects to generate free charges, light, heat, free radicals or carriers are the significant reason for the metal or inorganic nanoparticles to provide antiviral efficacy [73]. Under the visible light irradiation, Cu nanoparticles are able to exhibit surface plasmon resonance which are effective against viral infection via interface the replication or adhesion of the viruses on the surfaces [73,74]. In addition copper oxide (CuO) nanoparticles are semiconductor in nature. Thus, such nanoparticles have ability to produce reactive oxygen species such as  $\text{OH}^\bullet$ ,  $\text{O}_2^\bullet$ , hydrogen peroxide or some other type free radicals via the interaction with moisture or light. It has been reported that such free radicals are highly efficient to inactivate the single or double-strained DNA or RNA including enveloped or non-enveloped viruses and also bacteria on the Cu nanoparticles coated surfaces and prevented the virus entry [19,23,75,76]. The surface redox reactions between Cu nanoparticle coated surfaces and viruses are another potential way in order to restrain the proliferation viruses [73,75]. The generated reactive oxygen species and free radicals on Cu nanoparticles coated surfaces are highly effective against the SARSCoV-2 (by the disintegration of viral surface



**Fig. 3.** Schematic representation of antiviral efficacy of Cu—Ag nanohybrids based coatings against SARS-CoV-2 (after 1 and 5 min), breaking the SARS-CoV-2 transmission chains and containing the pandemic within the hospital and livestock settings, and in public reservoirs. Nanohybrids A and B represent samples 2 and 3, containing  $\sim 65$  and  $78$  wt% Cu and  $\sim 7$  and  $9$  wt% Ag, respectively Reproduced with permission from ref. [Mosselhy et al. [70], Copyright 2021, MDPI.

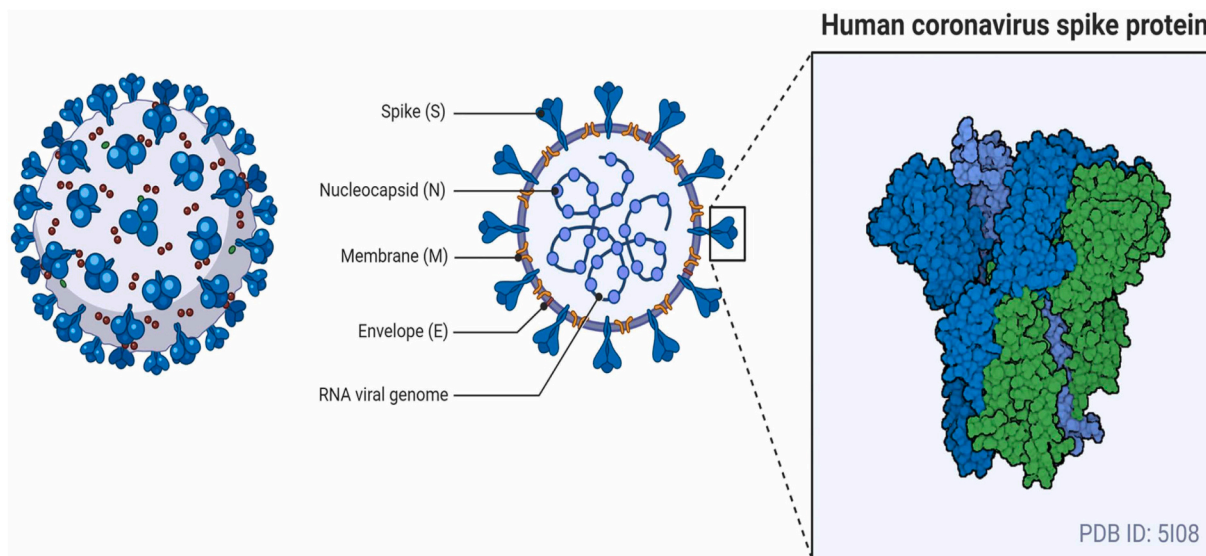


**Fig. 4.** (a) Schematic representation of synthetic pathway CuO nanoparticle synthesis, coating on cotton fabrics and evaluation of antimicrobial efficacy, (b) medical facility that could be help to inhibit the spreading of COVID-19. Reproduced with permission from ref. [71], Copyright 2022, Elsevier.



**Fig. 5.** (a) Scanning electron microscopy (SEM) images for (a) uncoated cotton fabric, (b) CuO coated cotton fabric, (c) CuO/starched cotton fabric, (d) CuO-Ag coated cotton. Reproduced with permission from ref. [71], Copyright 2022, Elsevier.

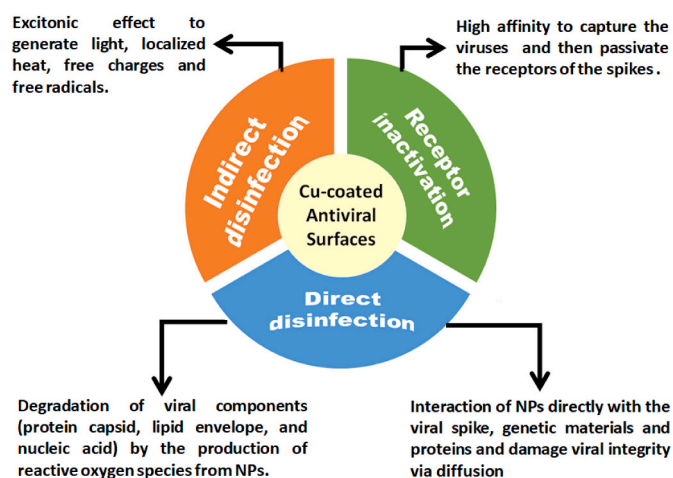




**Fig. 6.** Schematic representation of the structure of coronavirus along with description of four main structural proteins. Reproduced with permission from ref. [54], Copyright 2022, Elsevier.

spikes, genomes and degradation of viral proteins such as neuraminidase, hemagglutinin etc.) which is responsible for current ongoing pandemic of COVID-19 [23,75]. The “contact killing” phenomenon for SARS-CoV-2 also has been reported by Cu nanoparticles coated surfaces. Because of exceptional sensitivity of SARS-CoV-2 to Cu surfaces, the inactivation of such virus is reported by >99.99% within 1 min of contact on the surface of masks coated with copper oxide [75,77]. Behzadinasab et al. [75] also reported that coating of cuprous oxide particles along with polyurethane on the surfaces of glass slides and stainless steel exhibits by >99.99% inactivation of SARS-CoV-2 within 1 h as compared to uncoated surfaces. The author also observed that the combination of polyurethane and cuprous oxide coating adheres well not only on stainless steel and glass surfaces, also suitable for everyday items such as doorknobs, keypad button, credit card and pen which people may fear to touch during the adverse time of COVID-19 pandemic.

It has been also reported that functionalized copper nanoparticles coated surfaces like cotton fabrics, face masks or other personal protective equipment exhibited antiviral efficacy because of their high affinity to capture the viruses. Such surfaces resist the entry the virus into human cell by passivation of receptors spikes. For instance, Archana et al. [78] reported about coating of copper iodide on cotton fabrics by ultrasonication method. In this study, copper iodide was synthesized by the use of aqueous extract of Hibiscus flower as a source of reducing, stabilizing and capping agents. The coating on the surface of cotton fabrics was performed by the dip coating approach in the solution of copper iodide (1 mg/mL) in acetonitrile under ultrasonication for 30 min. Authors performed molecular docking study in order to evaluate the interaction of coated surface and COVID-19. From the experimental findings, it was observed that the cyanidin-3-sophoroside capped copper iodide particles based coating exhibited better binding affinity against COVID-19 main protease protein with  $-80.34$  kcal/mol minimum binding energy. Authors concluded that better binding energy of cyanidine-3-sophoroside bound copper iodide with the COVID-19 main protease protein will be useful in order to prevent the viral infection. Thus according to above literature discussion, the possible pathways by which copper nanoparticles act on different viruses to inhibit the transmission or viral entry are summarized in Fig. 7 [64,73].



**Fig. 7.** Possible pathways to exhibit antiviral efficacy of the Cu nanoparticles coated surfaces as viral entry inhibitors.

## 5. Concluding remarks and future perspectives

SARS-CoV-2 spread quickly with very high rate since at the end of 2019, and causes extraordinary risk to precious human life. Because of its contagious spreading nature, antiviral surfaces are urgently required from common public to medical healthcare persons in order to prevent or reduce the transmission of SARS-CoV-2. In this perspective, nanotechnology, particularly Ag, Ti and Cu nanoparticles (CuO, Cu<sub>2</sub>O, CuS etc.) based coating approach has provided innovative solution and made significant contribution in inactivation of SARS-CoV-2. Among these nanoparticles, copper nanoparticles based antiviral coatings against SARS-CoV-2 have been developed on various surfaces such as fiber, cotton, metals, glass and polymeric substrates including public places, people's homes, and health care settings for the safety of precious human life. Thus, results of the review study demonstrated that copper nanoparticles based coating could be effective and promising in the prevention contagious viral transmission. Charge-charge interaction generated of reactive oxygen species and excitonic effects are the significant mode of action of copper nanoparticles based coatings to inactivate the viruses within very short time of interaction. Besides having a



number of advantages in the copper based coatings as viral entry inhibitor in lab scale, considering the long-term stability of coating materials on the surface of applied substrates in real environmental conditions and toxicity of nanomaterial at large scale application are a matter of serious concern. Metallic nanoparticles have higher toxicity as compared to their bulk materials, thus safety and cytotoxicity of the metallic nanoparticles are the significant limitation at large scale application as coating materials. Therefore, it is highly essential to perform further research about short and long-term toxicity assessment of coated nanoparticles on environment and human health during large scale application. Moreover, virus inactivation time of most of the nanoparticles-based coated surfaces is needed longer time. Thus further optimization of key factor is essential to reduce the inactivation time for contagious viruses. Additionally, only few studies are reported in fabrication of antiviral coatings surfaces on various substrates which are commonly used in daily life applications. However, infection/transmission of some other pathogens is possible in coming future similar to the current ongoing infection of COVID-19. Thus, further studies based on development of nanoparticles coated surfaces with multiple viral inactivation efficacies are also recommended.

### 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 paper.

### Data availability

No data was used for the research described in the article.

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