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Review paper

Photocatalytic TiO_2 nanomaterials as potential antimicrobial and antiviral agents: Scope against blocking the SARS-COV-2 spread

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ABSTRACT

The whole world is struggling with current coronavirus pandemic that shows urgent need to develop novel technologies, medical innovations or innovative materials for controlling SARS-CoV-2 infection. The mode of infection of SARS-CoV-2 is still not well known and seems to spread through surface, air, and water. Therefore, the whole surrounding environment needs to be disinfected with continuous function. For that purpose, materials with excellent antiviral properties, cost effective, environmental friendly and practically applicable should be researched. Titanium dioxide (TiO_2) under ultraviolet light produces strong oxidative effect and is utilized as photocatalytic disinfectant in biomedical field. TiO_2 based photocatalysts are effective antimicrobial/antiviral agents under ambient conditions with potential to be used even in indoor environment for inactivation of bacteria/viruses. Interestingly, recent studies highlight the effective disinfection of SARS-CoV-2 using TiO_2 photocatalysts. Here, scope of TiO_2 photocatalysts as emerging disinfectant against SARS-CoV-2 infection has been discussed in view of their excellent antibacterial and antiviral activities against various bacteria and viruses (e.g. H1N1, MNV, HSV, NDV, HCoV etc.). The current state of development of TiO_2 based nano-photocatalysts as disinfectant shows their potential to combat with SARS-CoV-2 viral infection and are promising for any other such variants or viruses, bacteria in future studies.

1. Introduction

The current pandemic started in 2019–2020 due to the coronavirus i. e. COVID-19 (SARS-CoV-2) [1,2] has opened several questions for the scientific community. Scientists from biomedical, medicines, materials, engineering etc. are trying to understand the cause of its spreading worldwide and also much effort is being devoted on how to control it [1,3]. Vaccination against corona virus has been started already worldwide as one of the important steps for controlling the diseases and development of new methods as well as materials are under progress on international level. However, the spreading of virus is still a question [2,4] as second wave started in 2021 has become more dangerous with expectation of even worse condition of third wave according to the scientist from all over the world. Studies reveal that transmission of COVID-19 (SARS-CoV-2) including other viruses spread through direct and/or indirect contact via virus-containing airborne droplets or contaminated surfaces of objects, for example, floors, glass surfaces, windows, doors, handrails, touch panel/buttons, or furniture etc. [3,4]. Recent studies also reveal there is possibility of airborne transmission of SARS-CoV-2 virus [5–7]. This virus has been found to be highly contagious and can remain active for many days on the various surfaces [3,8,9] which is supposed to be the major source of transmission [9,10].

Although, the vaccines against SARS-CoV-2 have been developed [11–13] which can help in controlling the pandemic but it is at the initial stage of success with lots of uncertainty. Controlling the surface transmission of the virus may be more effective for slowing down the spread of its infection in public as in outdoor as well as indoor environments. Developing antiviral surfaces could be one of the promising ways to slow down the virus infection [3,8,9,14–19]. It can provide a potential technology for practical applications not only in hospitals but also in other public places to prevent the spread of the viruses and inactivation of the transmission of the viruses [18,19]. Several metal, semiconductor and nanocomposite materials have been used to develop antibacterial as well as antiviral surfaces for inactivation of bacteria or viruses [14,16,17,20–27]. Similarly, various nanomaterials surfaces made of metals, semiconductors, alloys have been proposed to combat with

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SARS-CoV-2 [2,3,8,9,18,28,29]. Antiviral nanomaterials based surfaces or coating which can effectively work in outdoor as well as indoor environment would be more promising for these purposes because the most infectious viruses are found nearby the patients in hospitals or home. In this sense, photocatalytic surfaces, could be more promising because they permanently oxidize, inactivate and destroy microorganisms under normal ambient lighting conditions i.e. are also effective in indoor environment [3,28,30,31]. Recent studies show great potential of the photocatalytic materials surfaces for the inactivation of SARS-CoV-2 [30,32,33].

Among various photocatalyst nanomaterials being used as antibacterial or antiviral materials, titanium dioxide (TiO_2) is one of the best photocatalysts well known for photodegradation of organic pollutants, photo induced bacterial and virus disinfections and self-cleaning properties [3,14–16,34,35] (Fig. 1). It is a promising photocatalyst due to its highly oxidizing ability of the chemical species adsorbed on its surface under ultraviolet (UV) light irradiation. Under the influence of UV irradiation, TiO_2 based photocatalysts produce highly oxidizing free radicals that are known to have bactericidal and antiviral action against several microbes and viruses including influenza, rotavirus and SARS-CoV-2 [30]. The photocatalytic activities are generally influenced by the structural and surface modifications that include specific surface area, particle shape, size, adsorption nature etc. [27,36–38]. Therefore, the engineering of materials shape and size is one of the important factor along with surface modifications by coupling with other functional antimicrobial/viral nanomaterials that effectively influence the photocatalytic efficiency [27,36,39,40]. Such TiO_2 based nanocomposite photocatalyst show visible light active photocatalysis and effectively work in outdoor as well as indoor (light and dark) environment for multipurpose actions as shown in Fig. 1. Due to these characteristics, TiO_2 is of great interest for disinfection of surfaces, air and water which could be surely useful in the inactivation of SARS-CoV-2 and controlling its transmission in human and environment [31,41–44]. Recent studies also show that TiO_2 NPs under UV exposure may cause adverse effects on human and environment via induction of oxidative stress resulting in cell damage, genotoxicity, inflammation, immune response etc., however, it is still controversial and detailed study is required [45–48].

Considering the above mentioned facts, the photocatalytic mechanism of TiO_2 nanostructures also needs to be explored in detailed against antibacterial and antiviral applications for better results in the environmental disinfection. This article covers the scope of photocatalytic mechanism of TiO_2 based photocatalysts towards antimicrobial/antiviral applications, against viruses in general and especially against SARS-COV-2 viral spread. In this short review, the role of TiO_2 as an excellent photocatalyst for bacterial and viral disinfection with emphasis on the antiviral activities against various viruses is briefly presented and discussed. In view of its photocatalytic activities with respect to organic matter, bacteria, viruses etc., the possible application

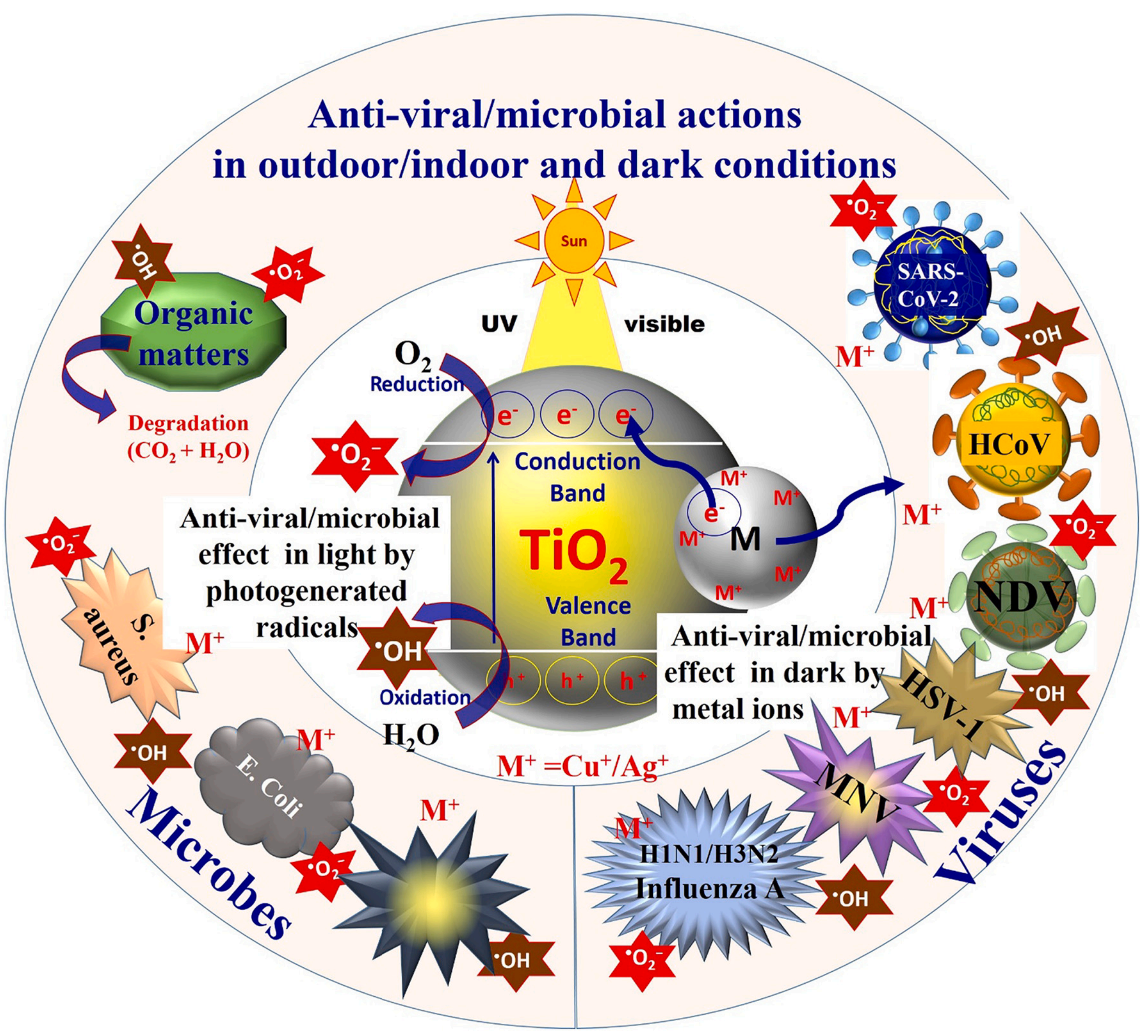

Fig. 1. TiO_2 based photocatalysts and their photocatalytic effect in degradation of organic matters, antimicrobial and antiviral effects against several microbes and viruses.

of TiO_2 based photocatalyst in designing an effective material for the inactivation of SARS-CoV-2 has been further discussed including the brief highlights about the recent progress in disinfection of SARS-CoV-2 using TiO_2 photocatalysts.

2. TiO_2 photocatalysts

TiO_2 is a semi-conductor metal oxide photocatalyst with a wide band gap of 3.2 eV and possibility to tune its bad gap characteristics [3,27,36,37]. TiO_2 exists in three different forms where, anatase structure is found to be more suitable for photocatalytic applications. [34]. Photocatalysis is a surface phenomenon, which oxidizes/reduces or degrades the organic pollutants, biomolecules, micro-organisms into environment-friendly CO_2 and H_2O in presence of a photocatalyst [36,49]. As shown in Fig. 2, TiO_2 when exposed to UV light of energy equal to or greater than its band gap, there is an excitation of electrons from valance band (VB) to conduction band (CB) of TiO_2. The photo-induced charge carriers; electrons and holes, are highly reducing and oxidizing in nature. These charge carriers move onto the surface of TiO_2. The charge carriers interact with the ambient oxygen (O_2) and water (H_2O) molecules. Holes oxidizes H_2O molecules into highly reactive hydroxyl radicals ($^{\bullet}OH$) and electrons reduces O_2 molecules to

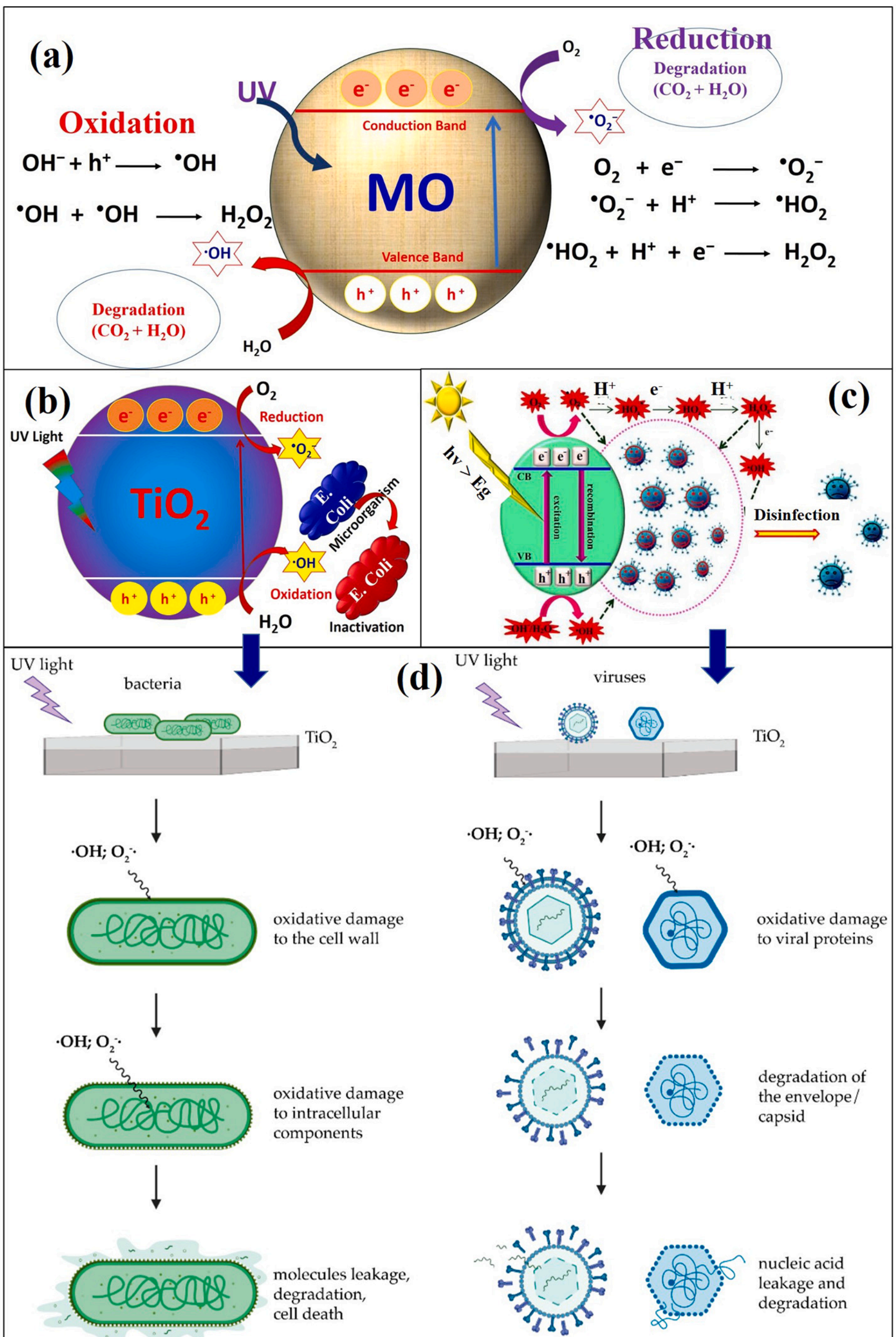

Fig. 2. ROS generation of $^{\bullet}OH$ and $O_2^{-}\bullet$ after UV light irradiation of TiO_2. Photocatalytic action of TiO_2 for photocatalytic (a) degradation of organic matters [39](b) antibacterial activity [27](c) antiviral activity. Reproduced with permission from [65] (d) Mechanism of photocatalytic inactivation of bacteria and viruses. [66].

superoxide radical anion ($^{\bullet}O_2^{-}$), which is further reduced to $^{\bullet}OH$. Since these radicals are highly reactive, thus known as Reactive Oxygen Species (ROS). These ROS, on the surface of TiO_2 reacts with harmful organic pollutants and results into its degradation to CO_2 and H_2O [27,36,39,49]. Photogenerated holes in the VB of TiO_2 exhibit strong oxidation power for decomposing organic matters and similarly photogenerated electrons in CB exhibit reduction process for decomposing organic matters as sown in Fig. 2a.

The photodegradation of organic materials using TiO_2 photocatalysts is extensively being implementing in the field of water, food and other environmental applications [27,50,51]. Extensive research has been carried out for the photocatalytic action in variety of research fields using TiO_2 based nanostructures under UV light activation. However, the wide band gap of TiO_2 photocatalyst restricts its functional activities beyond the UV region. In view of its biomedical applications such as disinfection in indoor applications, TiO_2 is not very suitable because it can only be activated by UV light, which is hardly contained in normal room light. For effective indoor or outdoor applications where less or more sunlight is available with only 3–5% UV radiation, TiO_2 has been modified through several ways to impart visible light activity to harness the maximum solar energy from visible to near infrared radiation such as doping using metal or non-metals, hybrid nanocomposite formation using functional nanomaterials (i.e. metal, graphene, semiconductors) etc. [37,39,40,52–58]. One of the important fact is that TiO_2 in nano-dimensional structures exhibit even better functionality as compared to its bulk TiO_2 material because of the enhanced surface area. Additionally, modification of TiO_2 induced by doping or nanocomposite formation using different functional nanomaterials provide synergistic effect of composed materials through defect production, structural/optoelectronic changes, trapping of light and improvement in surface charge transfer properties leading to the excellent visible light active material [27,36,59–64].

In case of microbes and viruses, components such as surface proteins are oxidized under UV irradiation when come in contact or closure to the surface of TiO_2 resulting in disinfection of microbes and viruses (Figs. 2 b-d) which have been discussed in detail in the next sections. Since, viral infections mainly occur in indoor environments, it is necessary to use a visible light-sensitive antiviral photocatalyst. In this regard, TiO_2 nanomaterials with visible light activity has been extensively investigated by modifying through various processes that includes, doping or coupling with other functional or antimicrobial nanomaterials [27,39,44,67]. It is also noted that lighting is usually turned off during the night; thus, the sustained antiviral properties of photocatalysts under dark conditions are also important for their practical applications [3]. Since, photocatalytic reaction needs the light to activate the process, so antiviral properties in the dark condition should come from something other than the photocatalytic properties. Therefore, use of other antimicrobial agents coupled with TiO_2 such as Cu, Ag and others not only enhance the photocatalytic disinfection in visible light for outdoor and indoor (less sunlight intensity) conditions but also can release ions that may effective for disinfection under the dark conditions [3,27,40,53,68–70].

The shape, size, and orientation of the nanocrystals of TiO_2 have also shown the effect on deactivating the microbial agents in the dark condition with no light present. In particular, nanostructured TiO_2 films composed of highly textured (004) anatase nanograins exhibited very high photocatalytic performance [38]. Such oriented nanograins have high Ti atomic density on its planes, which exhibited the strong bacterial killing even without the presence of UV light. This observation provides significant benefits for the nanostructured TiO_2 surface that can offer the antimicrobial properties even when the surface is not exposed to light or the light is not continuously supplied.

Another important aspect of using TiO_2 nano photocatalysts is to apply in thin film coating form which is very promising for the daily usable objects and places like hospitals or home for inactivation of microbes and viruses. The reason is that handling of nanopowder photocatalysts can arise many secondary problems such as separation of the photocatalyst from solution/suspension after photocatalysis reaction [34] and health concerns [71]. For the effective photocatalytic actions in outdoor/indoor locations and for potential applications in dark conditions by using other anti-microbial/viral agents such as Cu/Ag [72,73] as discussed above, TiO_2 based photocatalysts seem to be very promising and futuristic materials for controlling spread of viruses and their contaminations.

3. TiO_2 as antimicrobial photocatalysts

As discussed above, TiO_2 nanomaterials have extensively been used as photocatalysts in photodegradation of organic matter in water treatment. As a photocatalysts, disinfection of microbes/bacteria is another potential application of TiO_2 nanomaterials. In last decades, TiO_2 nanomaterials have been investigated for its antimicrobial effect against various microbes/bacteria in view of its promising utilization in disinfection of variety of surfaces along with purification of air as well as water [65,74]. TiO_2 has been studied in view of its disinfection effect for variety of microbes i.e. various Gram-negative/positive bacteria, fungi, algae etc. [74]. The mechanism of TiO_2 photocatalytic disinfection is still not so clear and a lot of debate is still going on for the exact mechanism of action. However, the killing mechanism is most accepted process of antimicrobial effect in which degradation of the cell wall/membrane mainly takes place due to the interaction of photoinduced ROS on the surface of TiO_2. This generally leads to leakage of cellular contents then cell lysis followed by complete mineralization of the organism. This process may involve various ways of disinfection. The ROS directly pierce the membranes of the microbes causing leakage of the cytoplasm leading to the death of cells. The ROS are strong oxidizing agents causing oxidative degradation of phospholipids and also take electrons forming fatty acid peroxy radicals affecting the functioning of the respiratory system leading to the death of microbes. Another way is that produced H_2O_2 undergo reaction and cleaved the guanine site of DNA leads to damage of the microbes [27,36,75–78]. Killing mechanism is known to be the most efficient process when there is close contact between the microbes and TiO_2 nanomaterials. Fig. 2b and d show schematics of antibacterial action of TiO_2 nanomaterial through generation of ROS and inactivation of bacteria under the UV irradiation.

There are several studies showing excellent antimicrobial activity of TiO_2 nanomaterials under the UV light irradiation [27,36,38,40]. The potential of TiO_2 nanomaterials has been extended to visible light through certain modifications for real practical application in indoor as well as outdoor places such as hospitals. TiO_2 nanomaterials based coatings provide an effective antimicrobial surface for medical implements thereby reducing the risk of hospital-acquired infections and have been studied for real practical applications in disinfecting medical devices, and surfaces hospitals [31,43,79–81]. Reid et al. [31] demonstrated the effect of TiO_2 photocatalytic antimicrobial coating at near-patient, high-touch sites in a hospital wards. It was found that the TiO_2 coated surfaces showed lower microbial burden than uncoated sites and concluded that photocatalytic TiO_2 coatings can reduce the bioburden of high-risk surfaces in the healthcare environment.

As also discussed above, the antimicrobial killing activity is more effective when TiO_2 is coupled with other effective antimicrobial agents such as Cu, Ag and Au [3,27,74–76,83,84]. For example, Leyland et al.

[44] demonstrated that doped TiO_2 anti-bacterial visible light active photocatalytic coatings could be used to combat hospital-acquired infections in light and dark conditions. They studied F-doped and F/Cu-codoped TiO_2 for antimicrobial activities under conditions of visible light irradiation as well in darkness. Co-doping of TiO_2 with Cu exhibited significantly improved antimicrobial activity relative to doping with F alone, both under visible light and in dark conditions attributed to the known toxicity of copper in dark towards the microbes. The codoped-TiO_2 showed greater antimicrobial efficiency under visible light irradiation than in darkness exhibiting role of Cu in enhancing the photocatalytic antimicrobial activity. It shows the potential of Cu to increase the yield of ROS for photocatalytic action. This codoped-TiO_2 coating was found to be active in visible light as well as in dark involving photocatalytic and a metal ion release mechanism [44].

Similarly, Ag-TiO_2 systems have been investigated for antimicrobial activities and excellent results have been reported for bacterial disinfection in light/ambient as well as in dark conditions due to the surface plasmon properties of Ag or antibacterial release of Ag ions respectively [27,40]. Weng et al. [82] synthesized the Ag-TiO_2 system with higher surface area which exhibited excellent antibacterial properties against microbes/MC3T3-E1 cells as shown in Fig. 3A. It was proposed that this system performed well as antibacterial agent even in dark. The mechanism of bacterial inactivation was explained as the transfer of electron from the bacterial membrane took place to the TiO_2 surface followed by

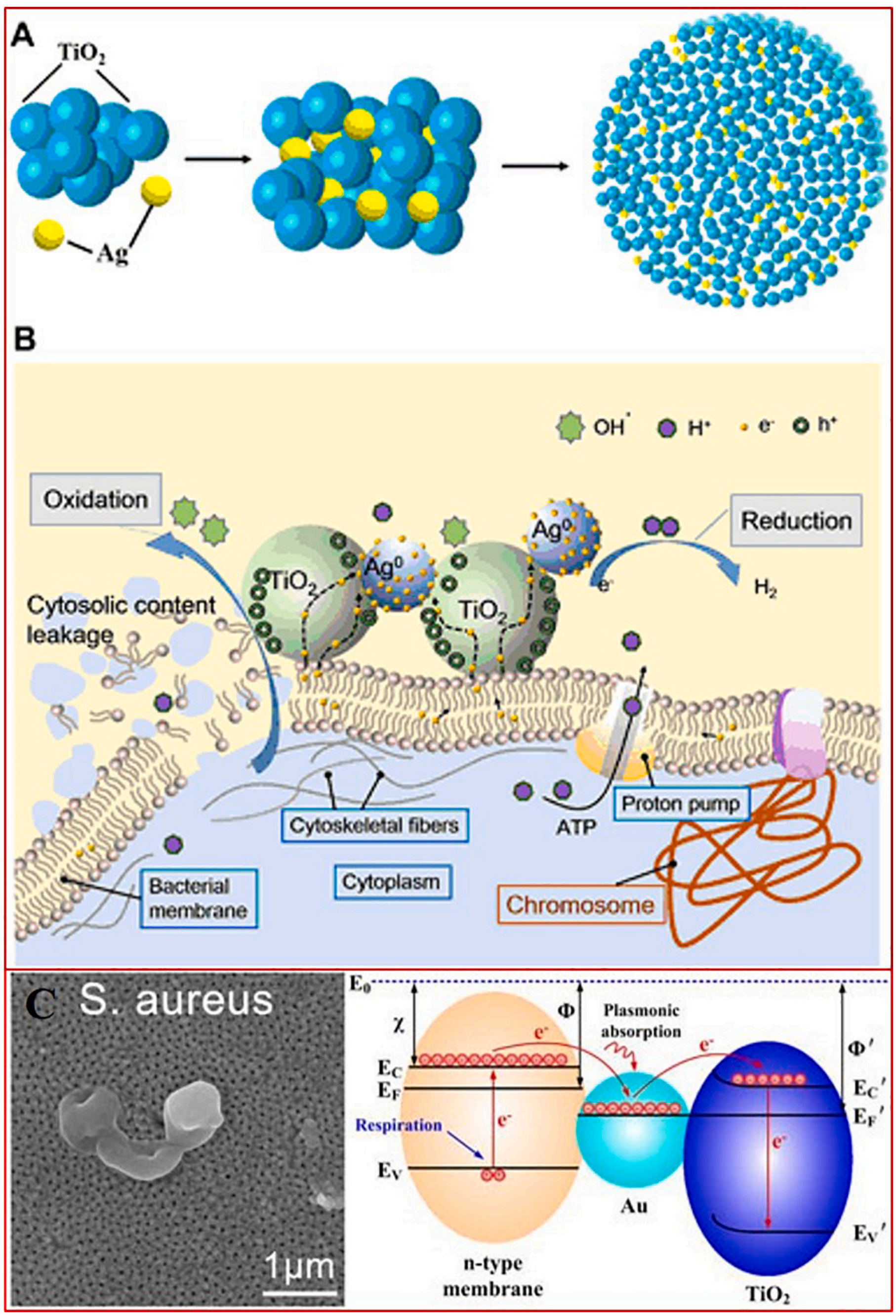

Fig. 3. (A) Schematic of preparation of Ag-TiO_2 microsphere system with higher surface area. (B) Schematic of antibacterial action of Ag-TiO2 system by electron transferring in the dark [82], (C) SEM micrograph of the *S. aureus* on Au-TiO_2 system and possible mechanism plasmonic Au NPs deposited on TiO_2 in dark conditions. Reproduced with permission from [83].

the Ag-TiO_2 interface due to the Schottky barrier effect (Fig. 3B). Similarly, Li et al. [83] proposed that Au–TiO_2 systems could be promising in killing microbes such as *E. coli* in darkness because of the surface plasmon properties of Au NPs deposited on the surface of TiO_2. It was proposed that respiratory electrons from the membranes of the microbes could be transferred to Au NPs and then to TiO_2 leading the microbes to steadily lose electrons until bacterial death as shown in Fig. 3C [27,83]. Such metal-TiO_2 composite systems based nanocoatings not only can provide better antimicrobial activity against microorganisms but also show promising self-cleaning/recyclable activities in presence of light (UV and visible) as well as in dark [40,85–88].

Very recently, Wasa et al., [89] proposed that TiO_2 nanostructured materials could be used as a coating on door handles and similar surfaces to reduce the viability and colonization by microorganisms stopping their spread. They studied antimicrobial and antibiofilm effect of TiO_2 nanostructured anatase, rutile and carbon (NsARC) coating against *E. coli*, *P. aeruginosa*, *S. aureus* and *S. cerevisiae* microorganisms. The results were also compared with antimicrobial effect on other surfaces such as stainless steel and copper under different conditions i.e., UV/visible light, ambient and dark conditions as shown in Fig. 4. Nanostructured TiO_2 coating NsARC surface found to be best with least survival of the microorganisms as compared to other uncoated surfaces

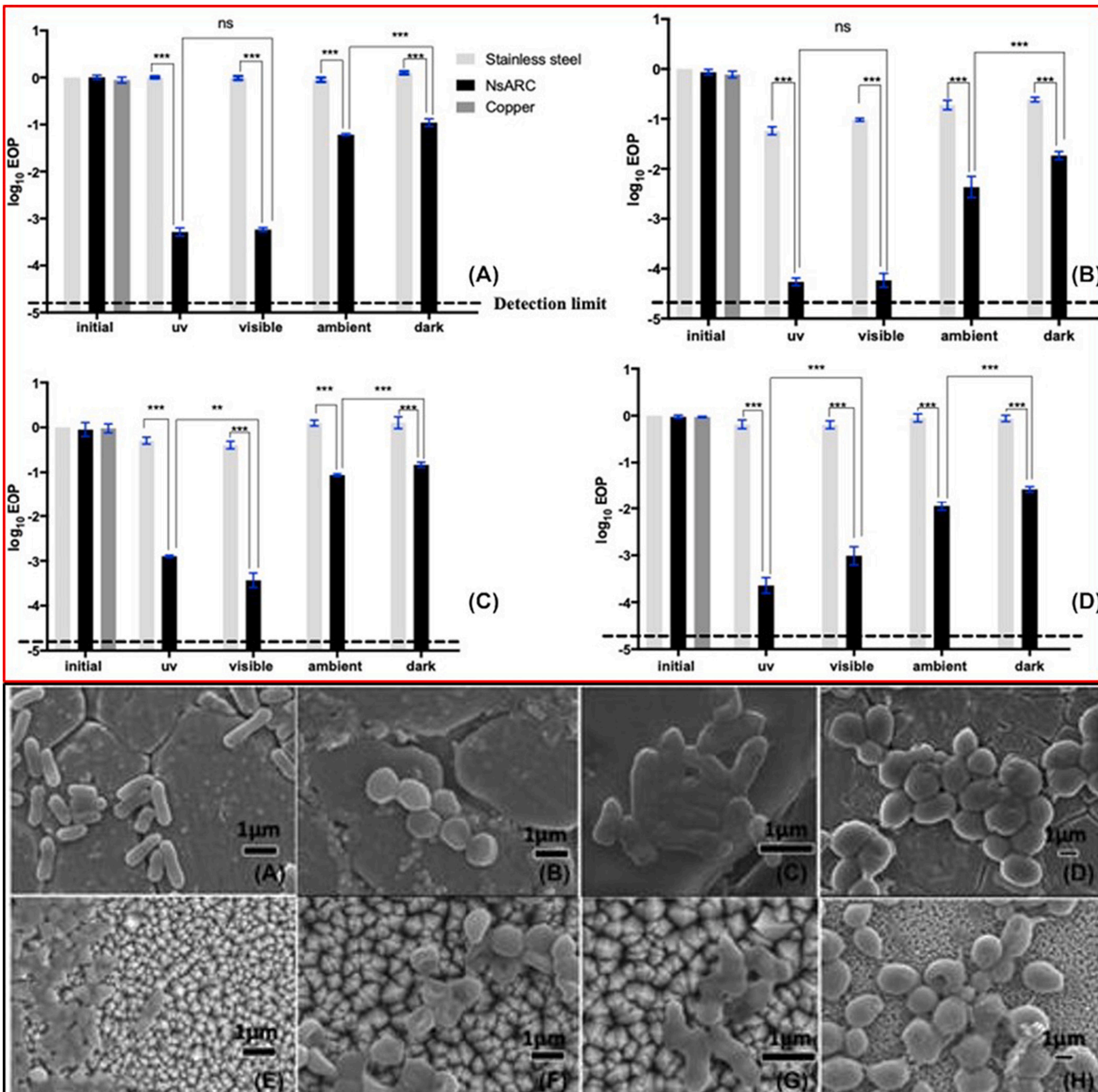

Fig. 4. (TOP-Graphs) Survival of **(A)** *E. coli*, **(B)** *S. aureus*, **(C)** *P. aeruginosa* and **(D)** *S. cerevisiae* on stainless steel, NsARC and copper after 8 h in the dark and exposure to UV, ambient and high intensity visible light. (* = $P < 0.05$; ** = $P < 0.01$; *** = $P < 0.001$; ns = not significant). (BOTTOM-SEM images): (A)-(D) corresponding SEM micrographs on stainless steel and NsARC surfaces for 8 h under high intensity visible light. Reproduced with permission from [89].

treated under all conditions. These nanostructure TiO_2 coating (NsARC) was also found to be very effective antimicrobial and antibiofilm even in the dark without light photoactication which was attributed to the antimicrobial activity of the carbon component of the NsARC. It is reported that carbon also acts as an antimicrobial and promising antiviral agent to combat with SARS-CoV-2 which can be potential candidate to use against SARS-CoV-2 when composite with TiO_2 based nanostructures [89,90]. Recent reviews also suggest that such antimicrobial nano coatings with significant antiviral activities can combat with various types of viral infections including SARS-CoV-2 virus [90–95].

4. TiO_2 as antiviral photocatalysts

As discussed so far, TiO_2 has gained much attention in last few years in the field of microbial remediation as a result of its powerful photocatalytic antimicrobial action towards different kind of microbes. Under the UV light exposure, the ambient oxygen and water decompose on the TiO_2 surface in ROS which act as a highly oxidizing or reducing agents causing decomposition of the organic and microbial matters. Further, modified TiO_2 has been found very useful in visible light activity in indoor or outdoor applications for disinfection of the surrounding. This photocatalytic disinfection effect has also been found to be very promising in controlling various viruses as antiviral photocatalyst [34]. The

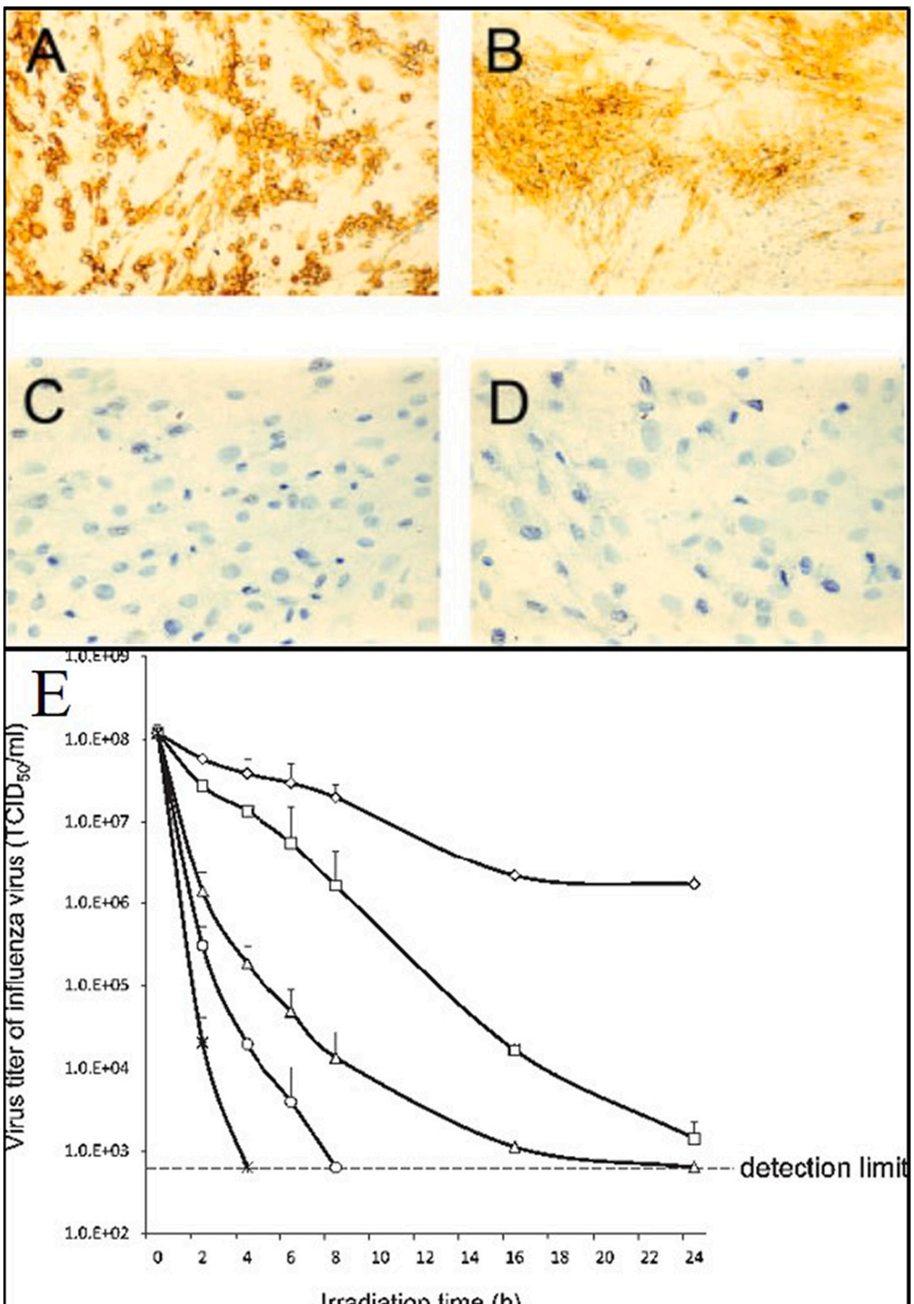

Fig. 5. Antiviral effect of TiO_2 films on HSV-1. (A) Control sample kept in dark; (B) control sample treated under UV light without TiO2 coating (C, D) with TiO_2 coating and under treatment of UV light. Reproduced with permission from [34]) (E) Time-dependent TiO_2-based inactivation of influenza virus under various UV-A intensities. [15].

ROS such as $^{\bullet}OH$ and $O_2^{-}\bullet$ which are produced at the surface of TiO_2 due to UV activation, are able to degrade the capsid/envelope proteins as well as the phospholipids of non-enveloped/enveloped viruses, respectively. Furthermore, due to the leakage and consequent nucleic acids degradation leads to the inactivation of the viral particles eventually as shown schematically in Fig. 2 [66]. Fig. 2c and d show schematics of antiviral action of TiO_2 nanomaterial through generation of ROS and inactivation of viruses under the UV irradiation.

Hojkova et al. [34] performed multifunctional photocatalytic effect of TiO_2 thin films including photodegradation of organic pollutants, antibacterial and antiviral effect. The photocatalytic degradation of dye molecules, *E. coli* and HSV-1 viruses (known as Herpes simplex virus) were investigated under UV irradiation. The antiviral effect of TiO_2 on HSV-1 viruses has been shown in Fig. 5 which showed the results of the replication of viral gC protein. The parts A and B in Fig. 5 show the dark brown color which is indication of replication of the virus in the LAP cells. Interestingly, it was found that the replication was achieved for both the virus stored in dark as well as treated under UV light. Figs. 5

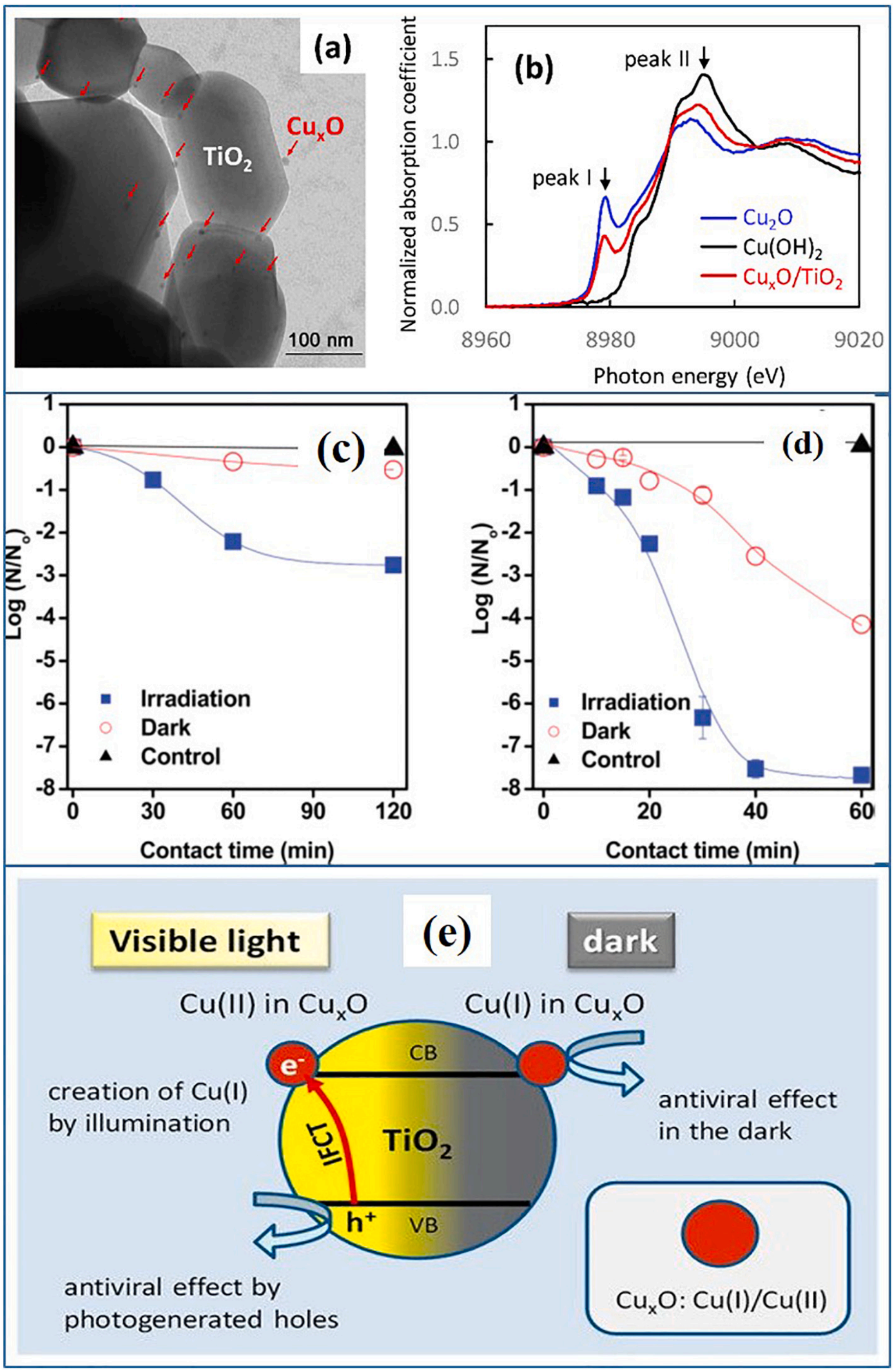

Fig. 6. (a) TEM image of Cu_xO/TiO_2 (b) XANES spectra of Cu_2O, $Cu(OH)_2$, and Cu_xO/TiO_2, Inactivation of bacteriophage Qβ under dark and visible-light irradiation. (c) 0.25% $Cu(II)/TiO_2$. (d) 0.25% $CuxO/TiO_2$ (CuI/CuII = 1.3). Reproduced with permission from [98] (e) Schematic illustration of the working principle of the antiviral Cu_xO/TiO_2 photocatalyst. [3].

C—D shows the antiviral effect of TiO_2 films indicating the absence of any such dark color which shows the complete loss of replication gC viral glycoprotein. This exhibits the full loss of virus ability to replicate on the LAP cells. It was found that TiO_2 thin films showed excellent antiviral effect against the viruses HSV-1 with 100% disinfection after 6 h of UV exposure. The antiviral effect of TiO_2 was attributed to the interaction of virus with the TiO_2 surface which brought significant changes in the virus structure resulting in the loss of virus ability to attack host cells. Akhtar et al. [16] demonstrated the antiviral activity of TiO_2) nanocolloids against Newcastle virus (NDV) attributed to the damage to the lipids found in viral envelop of the virus. Similar disinfection effects were observed on the different microbes using TiO_2 thin films/nanocolloids and concluded that these TiO_2 nanomaterials could be potentially used for developing new antiviral drugs. Nakano et al. [15] studied the inactivation of influenza virus using TiO_2 photocatalyst and found that TiO_2 showed excellent photocatalytic inactivation of the influenza virus through degradation of viral proteins and this depends on the intensity and time of UV irradiation (Fig. 5E**)**. Park et al. [14] investigated the antiviral effect of fluorinated TiO_2 (F-TiO_2) on human norovirus and several surrogates (MNV, FCV and MS2) under the UV light irradiation. Strong photocatalytic enhancement was observed effective in destroying the viruses under UV light due to the fluorination of TiO_2.

A strong antiviral activity of TiO_2-modified hydroxyapatite composite (HA/TiO_2) against H1N1 Influenza A Virus was reported under the UV light irradiation by Monmaturapoj et al. [96]. It was also concluded that such composites are promising for antimicrobial filtration applications for example, can be used in face masks. Similarly, Levina et al. [97] introduced TiO_2·PL–DNA nanocomposite consisting of TiO_2 NPs and polylysine (PL)-containing oligonucleotides for antiviral effect against H1N1, H5N1, and H3N2 subtypes of influenza A viruses. Miyauchi and colleagues [3,98] developed antiviral Cu_xO/TiO_2 photocatalyst with different valence states of Cu i.e. Cu(I) and Cu(II). X-ray absorption near-edge structure (XANES) and high-resolution transmission electron microscopic (TEM) results exhibited that Cu_xO clusters were composed of Cu(I) and Cu(II) valence states. These nanocomposite photocatalysts were found to be very promising for their functions in visible light as well as in dark attributed to the variable valence states of Cu. It was proposed that Cu(II) species present on the surface of TiO_2 nanoclusters withdrew electrons through photo-induced interfacial charge transfer leading to the formation of an anti-virus Cu(I) species and holes with strong oxidation power in the valence band of TiO_2 under visible-light irradiation. On the other hand, Cu(I) species showed antiviral effect in dark by denaturalizing the protein of the virus leading to the inactivation of the viruses (Fig. 6**)**. This is very promising result that shows the antiviral effect TiO_2 based photocatalysts in outdoor as well as indoor conditions. The Cu_xO/TiO_2 photocatalyst can thus be used to reduce the risk of virus infection by acting as an antiviral coating material [98].

Wang et al. [99] developed antimicrobial zero-valent nanosilver/titania-chitosan (nano-Ag^0-TiO_2-CS) filter bed for the removal and deactivation of airborne MS2 bacteriophage particles (viral aerosols). It was found that these composite systems were very effective for removing 93% of airborne MS2 particles and more than 95% of the MS2 could be efficiently deactivated in 20 min while using in an air purification system. On the other hand, Ag-TiO_2 nanocomposite coating was used for photocatalytic removal and deactivation of microbes and H1N1 virus [35]. The composite exhibited greater photocatalytic activity due to presence of Ag in UV as well as visible light irradiation with extremely high antimicrobial and antiviral effect greater than 99.99% against *E. coli* and infectious viruses. Similarly, Kozlova et al. [100] demonstrated the antiviral effect of TiO_2 and Pt-TiO_2 which showed better photocatalytic antiviral activity against vaccinia virus, and influenza A (H3N2) virus under UV light irradiation due to the presence of Pt. Pt-TiO_2 system was also reported to inactivate the viruses in dark.

The above discussion shows that TiO_2 based photocatalysts nanomaterials are very promising for antibacterial as well as antiviral activities. These TiO_2 photocatalysts have been used as coating in various public places like in hospitals to see the effect in ambient/light and also in the dark conditions and excellent antibacterial and antiviral action has been seen. Only TiO_2 is not efficient to work as antimicrobial or antiviral materials in dark conditions. However, its composites with other antibacterial or antimicrobial agents such as various metals provide promising protection from the microbes or viruses by inactivating them through release of ions. These characteristics of TiO_2 based photocatalysts show great potential to block SARS-CoV-2 spread which has been discussed in the next section including the recent developments in this field.

5. Emerging application of TiO_2 nano-photocatalysts against SARS-CoV-2

With increasing microbial and viral infections including the recent COVID-19 pandemic, there is an urgent need of multifunctional materials with antimicrobial as well as antiviral properties to combat with SARS-CoV-2 which could be potentially used in in hospital environments to stop the spread of infections arising from physical surfaces [17,34]. Rapid advances in developing antimicrobial and antiviral surfaces with excellent performance have been made in recent years. However, the new coronavirus infection has challenged the scientific community to think for new developments in the area of antimicrobial and antiviral. Furthermore, to stop the spread of such SARS-CoV-2 viral infections from one place to other through air, water and surfaces is another major challenging issue. To overcome these issues, development of new nanomaterials or new strategies to apply existing antimicrobial/antiviral nanostructured materials could be the promising way to combat with SARS-CoV-2 [90,101–103].

Since the earlier studies show that illumination of TiO_2 photocatalysts produces highly reducing/oxidizing free radicals with excellent anti-microbial/viral action against various microbes and also viruses such as influenza virus which are transmitted via aerosol and causes respiratory tract infection, similar to COVID-19 [102,104]. The photocatalytic effect of titanium apatite filter was used to show inactivation of SARS coronavirus long ago [104,105]. However, the antiviral efficacy of TiO_2 against SARS-CoV-2 is still to be investigated in details. The studies show that TiO_2 has a potential to combat SARS-CoV-2. There are a few studies carried out recently to investigate the effect of TiO_2 based nanomaterials in disinfection of SARS-CoV-2 [30,102,104,106]. Very recently, Khaiboullina et al. [104] demonstrated that TiO_2 NPs based photorespsive coating under the UV light exposure could be used as effective deterrent to the proliferation of COVID-19 surrogates and could play a major role to in destroying the viral particles. In a preliminary experiments, they explored the use of TiO_2 NPs in form of coating against inactivation of a close genetic relative of SAR-CoV-2, HCoV-NL63 under the influence of UV radiation Figs. 7 **(A-D).** In this work, the effect of UV irradiation was investigated on HCoV-NL63 viral genomic RNA stability. The treated viruses were investigated by quantitative RT-qPCR and virus infectivity assays after extracting total RNA.

Figs. 7A shows the results of copies of intact viral genomic RNA declined after UV light treatment of HCoV-NL63 virus at different UV irradiation time coated over glass surface. It was observed that with exposure of UV light irradiation, the degradation of genomic RNA of

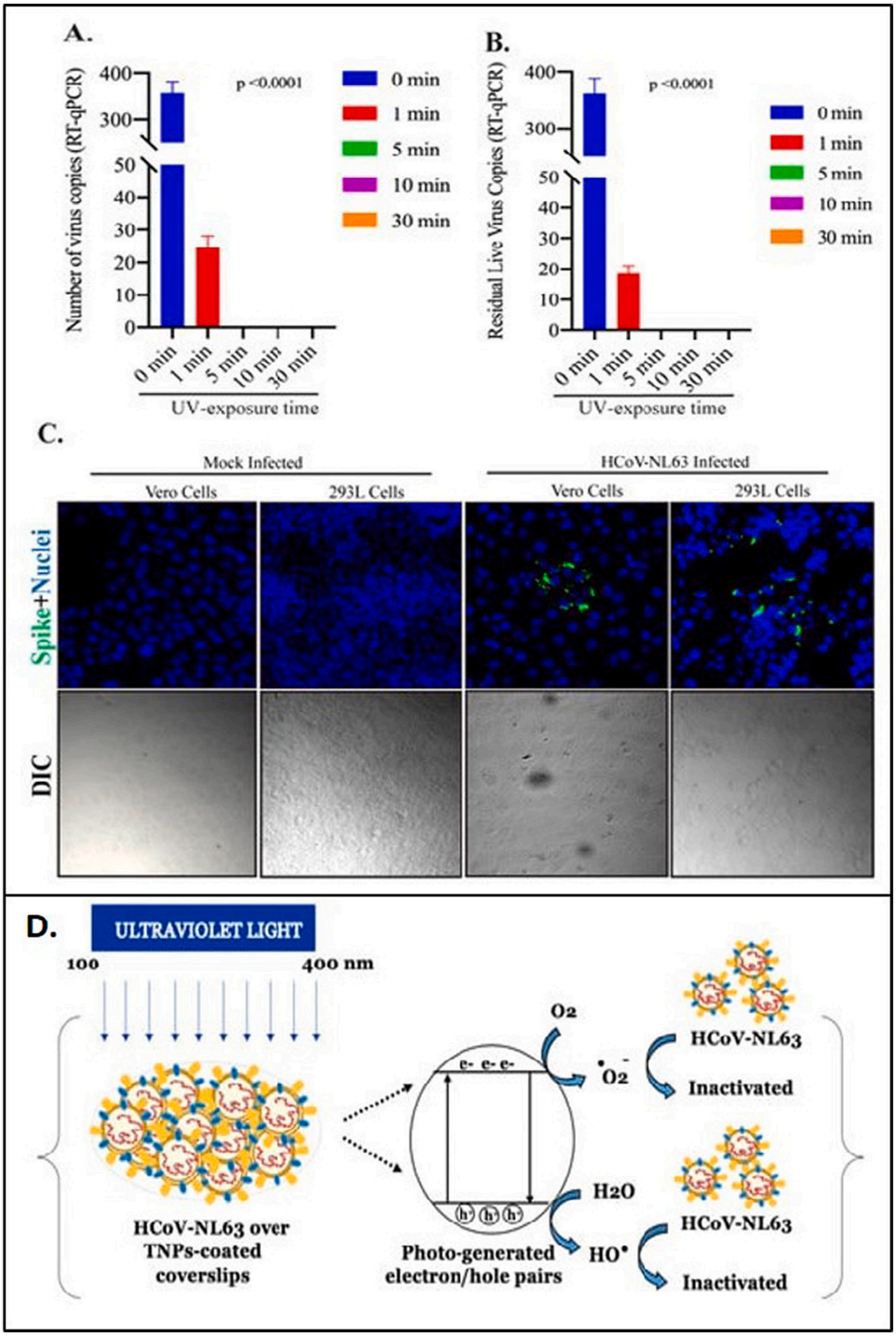

Fig. 7. HCoV-NL63 virus treated with UV light for time 0–30 min (A) on glass surface and examined using RT-qPCR, (B) examined for infecting HEK293L cells by placing on the monolayer of cells. (C) HCoV-NL63 viruses placed on monolayer of Vero E6 or HEK293L cells and incubated for 48 h for immunofluorescence assay. (D) Schematic illustration of photocatalytic inactivation of HCoV-NL63 principle. [104].

HCoV-NL63 cells increased and after 30 min of UV exposure, cells were completely degraded. Similarly, to investigate the infectivity of HCoV-NL63 virus after the UV treatment, these irradiated viruses were used for infection of HEK293L cells by placing over the layer of HEK293L cells. The results showed the complete disinfection of the viruses just after 5 min of exposure as shown in Figs. 7B. These HCoV-NL63 viruses were attached on the layer of HEK293L cells and incubated for 48 h and immunofluorescence assay was carried out. Also to study the

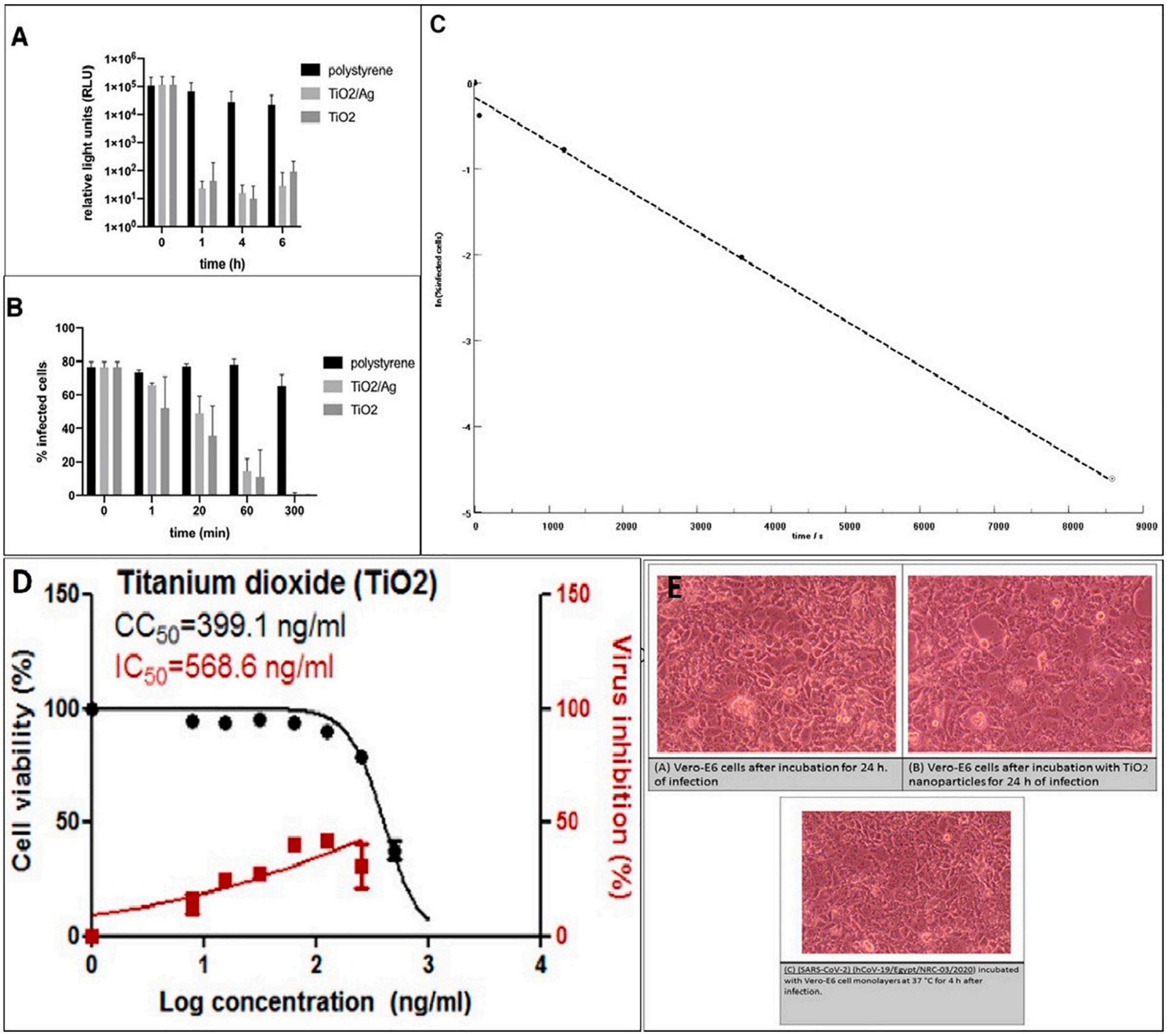

Fig. 8. Effect of Ag-TiO_2 and $Ti0_2$ coated tiles on (A) SARS-CoV-2 Spike pseudotype viral infection and (B) SARS-CoV-2 isolate REMRQ0001/Human/2020/Liverpool (C) Plot of the experimental data from (B) as ln(%infected cells) Vs time (s). The disinfection rate coefficient could be obtained from the slope. [30] (D) Plot of cytotoxicity/inhibitory concentration of TiO_2 NPs against SARS-CoV-2 activity, (E) (A–C) Images for Vero-E6 host cells (After infection) after the incubation with SARS-CoV-2 and treated with TiO_2 NPs. [106].

morphologies of the cells after incubation with UV treated viruses, differential interference contrast (DIC) imaging was carried out (Fig. 7C). The results exhibited a strong antiviral effect of TiO_2 NPs coated over the glass surface against HCoV-NL63 virus after the UV treatment attributed to the photocatalytic generation of ROS with strong oxidative capability to disinfect the virus by oxidative damage as shown schematically **in** Fig. 7**D**.

Micochova et al. [30] studied the stability of both SARS-CoV-2 Spike pseudotyped virions based on a lentiviral system, as well as fully infectious SARS-CoV-2 virus using TiO_2 based thin coatings of TiO_2 and Ag-TiO_2 nanocomposites on the ceramics tiles. The coated surfaces were inoculated with SARS-CoV-2 and treated under the ambient laboratory light conditions. The pseudotyped viral titer was found to be decreased by 4 orders of magnitude for both type of coatings. For live SARS-CoV-2 on coated tile surfaces, fully inactivation was observed only after 20 min of light exposure and no detectable active virus was found after 5 h of treatment. Significantly, SARS-CoV-2 on the uncoated tiles were found to be fully infectious at 5 h post-addition of viruses. Overall, the coated tiles 120 days previously were able to inactivate SARS-CoV-2 under ambient indoor lighting with 87% reduction in titres at 1 h and complete loss by 5 h of exposure (Fig. 8 A-C). It was concluded that in view of emerging SARS-CoV-2 with increased transmissibility, TiO_2 coatings could be an important tool in combatting SARS-CoV-2, particularly in health care facilities where nosocomial infection rates are high. Similarly, Negrete et al. [32] demonstrated the excellent photocatalytic effect Ag-TiO_2 nanomaterials of elimination of SARS-COV-2 after 9 h of exposure of UV light.

Different TiO_2 nanostructures such as NPs, nanotubes (NTs) and nanowires (NWs) etc. have also been studied and engineered for the enhanced photocatalytic antimicrobial and also antiviral effect to inactivate viruses including SARS-COV-2 virus with great efficiency. Hamza et al. [106] studied the effect of TiO_2 NTs for the disinfection of SARS-CoV-2 which exhibited strong anti-SARS-CoV-2 activity at very low cytotoxic concentrations in vitro with a non-significant selectivity index ($CC50/IC50 \leq 1$) along with excellent antiviral activity at a very low concentrations ($IC50 = 568.6$ ng/mL). It was concluded that these TiO_2 nanostructures are suitable for coatings as a potent disinfectant to combat SARS-CoV-2. As shown in Figs. 8 D-E, the SARS-CoV-2 cells when treated with TiO_2 NPs exhibited much enlarged patches around SRAS-CoV-2 cells which demonstrate the capability of the TiO_2 nanostructures to inactivate and inhibit the growth of the cells. Significantly, Vadlamani et al. [107] recently developed a electrochemical sensor

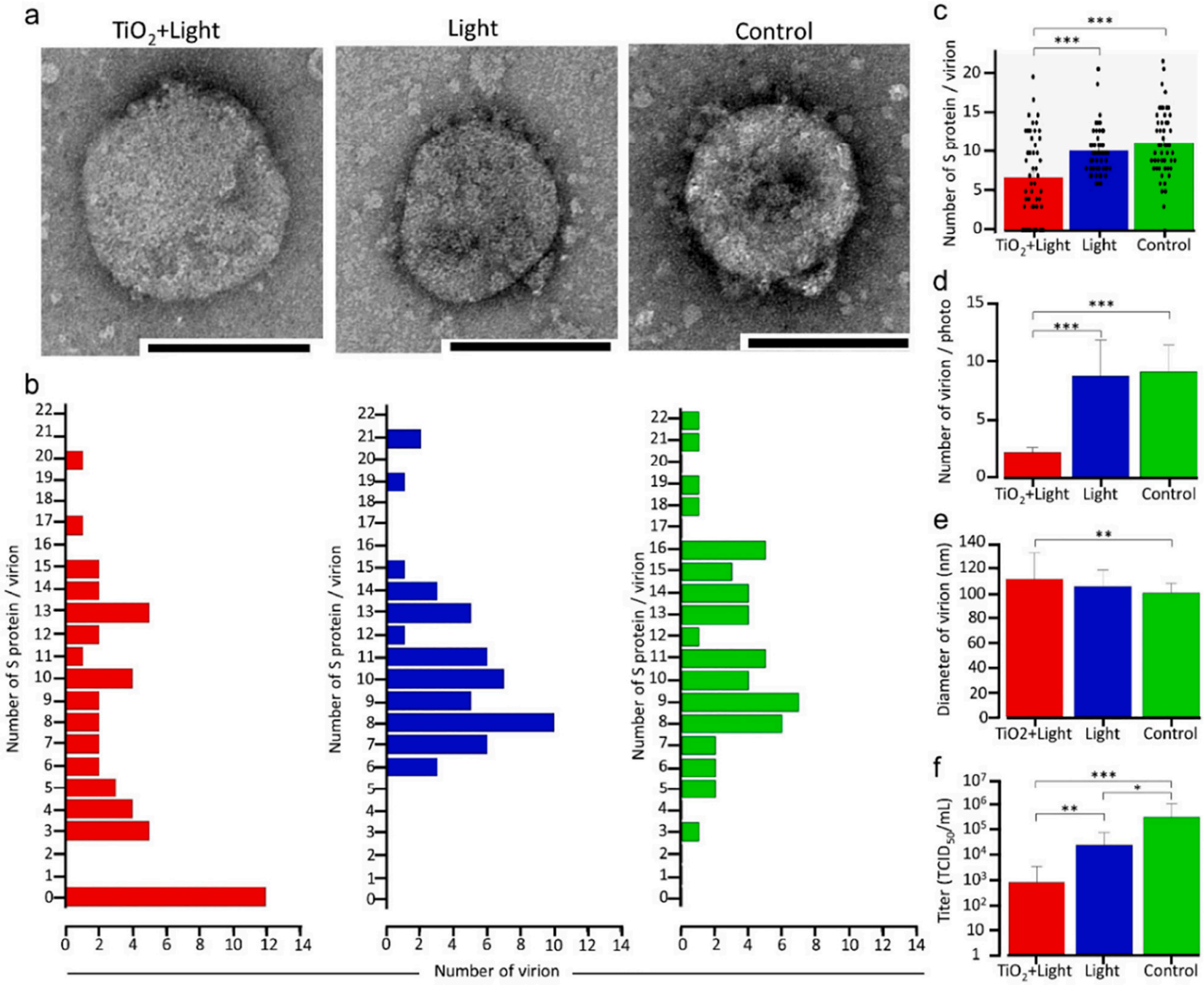

Fig. 9. TEM images: effect of LED and photocatalytic reactions on the morphology of SARS-CoV-2 virion morphology. (a) SARS-CoV-2 (Bar = 100 nm). (b) Plot of corresponding number of S proteinson single virions taken from TEM images of (a) (c) Each dot represents a value of S protein of each virion in (b). (d) Virion number in an area of 170 μm^2 in an individual TEM image is shown, $n = 10$. (e) Diameter of single virion. (f) Viral titer. Asterisk indicates a statistically significant difference (* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$). [102].

based on TiO_2 NTs for the rapid detection of SARS-CoV-2. Surface engineering of TiO_2 nanostructures has been proposed to tune its potential functionality for real applications in the battle with SARS-CoV-2 virus. Horváth et al. [108] developed TiO_2 NWs based filter to be used for personal protective equipment (PPE) and also for a new generation of air conditioners and air purifiers. These NWs were tested for photocatalytic generation of high levels of ROS by UV exposure with excellent antimicrobial and antiviral activities along with enhanced wettability by the water droplets carrying the germs. A prototype was proposed using these TiO_2 NWs coated mask with possibility of tuning the filter pore sizes by introducing TiO_2 NWs into filter paper. Using such nanostructures, it could be a promising way to produce easily sterilizable and reusable masks with excellent antiviral properties to be used as a potent prevention tool against the rapid spread of SARS-CoV-2 and other coronaviruses [108].

Interestingly, Matsuura et al. [102] recently demonstrated that TiO_2 coating could be effective in inactivating SARS-CoV-2 through the TiO_2-mediated photocatalytic reactions in a time-dependent manner and studied through the microstructural change observed in SARS-CoV-2 virus using transmission electron microscopy (TEM) (Fig. 9). The antiviral activity was performed in aerosol and liquid which was found be very effective upto 99.9% after 20 min of interaction with coating. The mechanistic effects of TiO_2 photocatalyst on SARS-CoV-2 virion included decreased total observed virion count, increased virion size, and reduced particle surface spike structure. Other things like TiO_2 photocatalytic damaging of viral proteins and genome were also studied using western blotting and RT-qPCR, respectively. It was concluded that TiO_2-induced photocatalytic reaction is promising and potential for disinfection of SARS-CoV-2 and other emerging infectious disease-causing agents in human habitation.

The results discussed above show the very recent studies for inactivation of SARS-CoV-2 viruses using various TiO_2 based nanomaterials. The photocatalytic mechanism of TiO_2 nanostructures has been explored for disinfection of SARS-CoV-2 and found every effective for antiviral applications. Interestingly, these nanomaterials are also found to be very effective for ambient and dark conditions to be used in normal places when modified with other functional nanomaterials. This ability of TiO_2 based nanomaterials shows that there is a good scope of using photocatalytic mechanism of these photocatalysts towards antiviral applications not only for SARS-COV-2 viral infection but also for many general viral infections which spread in the normal environment.

6. Summary and outlook

The present world is fighting against coronavirus pandemic indicating the urgent need to develop novel or innovative materials for controlling the SARS-CoV-2 virus infection. The present review deals with the development of TiO_2 based photocatalysts with excellent antiviral activities and their emerging application in fighting against COVID-19 pandemic. The TiO_2 based photocatalysts are being used for multipurpose in the field of energy, environment and biomedical. In the field of biomedical, these photocatalysts are mainly used as an antibacterial or antiviral agent.

The recent advancements in the research related to their applications in ambient conditions for disinfection purpose provide significant results with improvement in their disinfection activities against viruses and microbes. These results indicate that TiO_2 photocatalysts are promising materials to be used for disinfection applications in open or close environments. TiO_2 itself with modification in shape/size and also modified TiO_2 with some other anti-bacterial/viral agents like metals are very effective for such purposes. Rigorous and systematic investigations are required to optimize their effectiveness with reference to their composition and activation under long range light radiation (UV to IR to cover the normal sunlight) including dark conditions. The major challenge in

this direction is to use these photocatalysts in the proper way such as in the form of coating on the various objects as well as surfaces of uses in different places. Recent reports reveal that antimicrobial and antiviral properties of TiO_2 based photocatalyst could be possibly tuned to be maintained even under the indoor (under the ambient and dark) conditions by surface coating and engineering. This has to be investigated on the practical level for real applications in various public places. It is expected that due to such promising and tunable characteristics, TiO_2 photocatalyst based nano coating can be applied to the surface of objects that are frequently used by the public (mask, air filters, gloves etc.), surfaces of the common places such as hospitals, home, airports, metro stations, and schools etc. to inactivate/stop the spreading/transmission of corona and other viruses.

Declaration of Competing Interest

Authors have no conflicts of interest.

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