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REVIEW ARTICLE

Review on inactivation of airborne viruses using non-thermal plasma technologies: from MS2 to coronavirus

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Abstract

Although several non-thermal plasmas (NTPs) technologies have been widely investigated in air treatment, very few studies have focused on the inactivation mechanism of viruses by NTPs. Due to its efficiency and environmental compatibility, non-thermal plasma could be considered a promising virus-inactivation technology. Plasma is a partly or fully ionized gas including some species (i.e., electrons, free radicals, ions, and neutral molecules) to oxidize pollutants or inactivate harmful organisms. Non-thermal plasmas are made using less energy and have an active electron at a much higher temperature than bulk gas molecules. This review describes NTPs for virus inactivation in indoor air. The different application processes of plasma for microorganism inactivation at both laboratory and pilot-scale was also reviewed This paper reports on recent advances in this exciting area of viral inactivation identifying applications and mechanisms of inactivation, and summarizing the results of the latest experiments in the literature. Moreover, special attention was paid to the mechanism of virus inactivation. Finally, the paper suggests research directions in the field of airborne virus inactivation using non-thermal plasma.

Keywords Non-thermal plasma · Virus inactivation · Indoor air · Best-advanced oxidation

Introduction

Viruses are part of the life history on our planet and the most abundant and diverse microbes. These species dwelled in the World for billions of years and infected all cell-based life forms organisms, i.e., from bacteria to humans, animals, and plants (Couch, 1981). Consequently, they are responsible for numerous hospitalizations, animal diseases, deaths, and crop losses, leading to immense social, economic, and biological pressures (Filipić et al. 2020a). They have adapted to various climates and are now found in all environmental compartments, such as the air, where the risk of infectious respiratory diseases is higher than any other sources (Tregoning and Schwarze, 2010). A viral respiratory infection could be exposed to bacterial disease, thus duplicating the risk of death (Hament et al. 1999). Despite considerable public health efforts, epidemics of viral respiratory infections are still common (widespread) in healthy humans and can lead to the death of vulnerable people (Moriyama et al. 2020). In 2017 alone, the Global Burden of Disease study found that air pollution is a fatal source of nearly 5 million premature deaths (Xiao et al. 2020). Also, another study via the World Bank in 2007 found that air infection diseases kill 750,000 people annually in China (Chang, 2012).

Typically, viruses exist in the air at specific concentrations, which are not generally sufficient to cause disease in humans because the immune system of healthy humans prevents infections. However, the risk of human contamination rises significantly at higher infectious virus concentrations (Nikitin et al. 2014). Numerous epidemiological studies

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demonstrated that air transmissions via aerosols, large droplets, or direct contact with secretions lead to a substantial increase in human morbidity and mortality, making air the most significant vector of viral infection (Couch 1981; Martínez-Montelongo et al. 2020. Pollution of indoor and outdoor air has been identified as responsible for significant deleterious effects on human health and social and economic growth (Martínez-Montelongo et al. 2020). However, indoor air pollution is the primary concern as it is 2–5 times more polluted than outside air pollution; in extreme cases, it can be over 100 times higher (Fang et al. 2016). Also, indoor environments often harbor potentially unsafe microorganisms (La Giuseppina et al. 2013).

Pandemics such as the COVID-19 established the necessity for indoor air cleaning and air purification techniques (Kim and Jang 2018) and replacing, completing, or updating existing conventional viral inactivation methods (Li et al. 2020). Most decontamination processes commonly used for viral inactivation like photocatalysis (TiO_2 + UVA) and filtration do not have an effective disinfection ability against viruses and have substantial inconveniences (Zhang and Gamage, 2010). Indeed, the most applied technologies to control and remove airborne pathogens are the collection of bioaerosols on filters, such as porcine reproductive and respiratory syndrome (PRRS), high-efficiency particulate arrestance (HEPA), minimum efficiency reporting value (MERV) 14 and MERV 16 filters, UV germicidal irradiation (UVGI), atmospheric pressure non-thermal plasmas (APNTP), and cold atmospheric pressure plasma (CAPP). HEPA filtration has been experienced to be very effective in removing bioaerosols from airstreams. In contrast, MERV filters were exhibited to be the safer choice for both roof bolter and face drill.

Indeed, Farnsworth et al. showed the highest efficiency (i.e., 96.5 ± 1.5%) of the bacterial collection of *Baccilus subtilis* by HEPA filtration. Alonso et al. reassessed the impact of air filtration from commercial sow farms on the incidence of PRRSV introductions. They found that air filtration resulted in a reduction of approximately 80% of the risk with introducing the new PRRSv, thus highlighting the role of PRRSv in aerosol filtration of the air. Otherwise, using HEPA filters denotes several disadvantages, such as high filter replacement costs, and high-pressure drops and increased energy consumption to maintain the desired ventilation rate (Amissah (2005), Tellier (2006), Tellier (2009)).

Likewise, HEPA filters do not deactivate pathogens, hence the possibility of re-emitting more resilient pathogens into the ambient air during the filter replacement and disposal processes. Effective UVGI disinfection requires enough high illumination intensity, achieved via an association of several bulbs with suitable exposure times in a well-designed airing system. However, the application of UVGI in the disinfection of indoor air is limited through the necessity to avoid the harmful effects of UV on human and animal health. One of those drawbacks is contamination with by-products of disinfection with carcinogenic effects and environmental pollution (Su et al. 2018). Unlike those chemical methods, NTPs, also named cold plasma (CP), entered the decontamination processes as a new, effective, clean solution for inactivating the virus (Lacombe et al. 2017). NTP is a complex mixture, consisting of a partially ionized gas containing high-energy photons (UV), free electrons, ions, radicals, and other reactive species (Assadi et al. 2015; Jia et al. 2015; Schmidt and Jo 2015; Jiang et al. 2017; Schiappacasse et al. 2020). It produces high-energy electrons which bump gas molecules, driving their dissociation, excitation, and ionization (Huang et al. 2018), thereby occurring many reactive oxidative species (ROS) including $^{\cdot}OH$, O_2^-, O_3, and H_2O_2. This ROS may effectively inactivate viruses (Li et al. 2020), as well as nitrogen species (NS) which play vital roles in virus inactivation (Wang et al. 2016). It is one of the advanced oxidation technologies proven effective in biomedical fields, including decontamination and sterilization, due to its low cost, easy operation, and wide range of applications (Feng et al. 2020). It is also essentially clean and generates only small amounts of persistent chemical species (Moreau et al. 2008). Few papers report NTP as an antiviral treatment in the air, yet it shows great promise and has proven to inactivate many types of microorganisms such as airborne viruses (Gallagher et al. 2004; Scholtz et al. 2015). For instance, NTP inactivation of coronavirus (COVID-19) (Chen and Wirz, 2020), Newcastle disease virus (NDV) (Su et al. 2018), and avian influenza virus (AIV) (Wang et al. 2016) have been successful. Thus, strategies should continue to be developed to improve NTP-based technologies to battle viruses for humanity's long-term benefit.

This review focuses on NTPs for the inactivation of viruses in indoor air. It is an attractive advanced oxidation technology since it is a new, effective, clean solution for inactivating the virus and presents recent advances in the exciting area of virus's inactivation, identifying applications and inactivation mechanisms, and summarizing findings in the latest literature experiments. An enumeration of the worldwide problem related to airborne viruses is cited. The effect of key operating parameters on NTP plasma techniques used in the literature is developed.

Viruses in indoor air

The term "indoor" includes all enclosed spaces occupied by humans such as homes, offices, schools, workplaces, commercial units, airports, hospitals, other health facilities (Moreau et al. 2008). According to the Environmental Protection Agency (EPA), many people spend about 90% or more (i.e., most of their time indoors) (Chen et al. 2020).

People spend more time at home than in any other indoor environment (Scholtz et al. 2015). Also, indoor air pollution is 2–5 times more polluted than outside air pollution. In extreme cases, it can be over 100 times higher (Chen et al. 2020) because of the various sources of indoor chemical pollution like formaldehyde from wood and biologic pollution (Anderson and Albert 1998). Besides, a study estimated the total concentrations of viruses in indoor air and found about 10^5 particles m^{-3}, which is an extremely high concentration (Chen et al. 2020). Environmental Protection Agency (EPA) ranks indoor air pollution as one of the top 5 environmental hazards and health threats, improving indoor air quality (IAQ) to reduce sickness. IAQ is the field of applied science or analysis of indoor air conditions that includes the viral, microbiological, and chemical-physical composition in the air in and around buildings (Maisey 2012). The definition of acceptable IAQ is provided by standard ISO 16000 "air in confined environments" in particular ISO 16814: air in an internal building which does not displease the vast majority of people inside to ensure them healthy conditions and is unlikely to contain pollutants leading to a risk to exposure to health (Prussin et al. 2015). The World Health Organization (WHO) stated that IAQ is essential for preserving human health.

Indoor air quality has a significant impact on human health status. Therefore, WHO concluded that it is the human right to breathe healthy indoor air. It is, therefore, the responsibility of all those involved to ensure acceptable indoor air quality. It becomes just like an invisible killer (World Health Organization 2000). According to China Standardization Association, 68% of illnesses are caused by poor indoor air quality (Vohra et al. 2006). In addition, some authors reported that higher disease and mortality rates are linked to air pollution and poor indoor air quality [46]. Yet, exposure to air pollutants can increase the susceptibility and severity of respiratory viruses in indoor air. Most upper respiratory infections (URIs) like cold, pneumonia, pharyngitis, laryngitis, and epiglottitis are caused by over 200 different viruses, including influenza viruses, rhinoviruses, coronaviruses, adenoviruses, respiratory syncytial viruses, and enteroviruses (US EPA, 2006). Recently, other viruses emerged at the end of 2019, such as SARS-CoV-2, killing millions of people worldwide, thus demonstrating the dangerousness of infectious respiratory diseases. Due to their high airborne transmission ability, inhaling these viruses can cause or worsen disease in humans (Rahmani et al. 2020), especially in crowded and poorly ventilated environments. They are responsible for most upper respiratory infections (Cimbala 2003). Many of the illnesses associated with SARS-CoV-2 that increase the risk of death are those caused by long-term exposure to air pollution (Xiao et al. 2020). Indoor virus species is one of the most common environmental health problems reported today (Table1). Exposure to aerosols generated by coughing and sneezing from infected individuals or in contact with droplet-contaminated surfaces (plastic, metal, and clothing) has been widely viewed as the dominant mode of transmission of respiratory pathogens (virus and bacteria). In addition, it has been validated that airborne transmission is traditionally defined as involving the inhalation of infectious aerosols primarily at a distance of less than 1 to 2 m from the individual carrying the virus. Such transmission has been reported, and considered as the main route of virus transmission. However, recently airborne transmission of many respiratory viruses has been validated, such as coronavirus (SARS-CoV), Middle East respiratory syndrome (MERS)-CoV, and influenza virus (Wang et al. 2021).

Viruses such as the coronavirus (i.e., SARS-CoV-2) are intracellular parasites that are very small in the range of 20 to 400 nm. These viruses are resistant to indoor air for a long time, especially in crowded or small environments. Inhaling these viruses causes illness or worsens infections of the upper respiratory tract (Prussin et al. 2015). In the event of a viral pandemic, many countries implement containment measures to prevent the spread of the virus. Still, this practice induces poor indoor air quality, which will lead to other health problems. Indoor air in enclosed public spaces is at increased risk of viruses because IAQ regulations are not adapted to current scientific research. So, viruses can spread through the air and even easily enter indoor air (World Health Organization 2000). Once locked in, even simple actions like talking, sneezing, and coughing that cause small virus-filled droplets of saliva to spread through the air and onto surfaces, especially on the hands (Alshraiedeh et al. 2013). Viral infection can spread from person to person, making humans a significant source of indoor viral infection. Pets are also a foremost source of indoor air contamination. Viruses can infect all living cell-based organisms, from bacteria to humans, animals, and plants (Filipić et al. 2020a, b).

Indoor air humidity is a major determinant of indoor air quality (Sakudo et al. 2014). It plays an important role in viral infections by promoting the survival rate of viruses and an increased risk of respiratory infections and allergic diseases (Aboubakr et al. 2018). Several studies demonstrated that indoor temperature and humidity (generally between 19 and 26 °C and 50–60% RH) positively affect the spread of infections and the vulnerability of individuals to viruses (Liang et al. 2020).

Pandemics such as COVID-19 require implementing new indoor air purification techniques (Kim and Jang, 2018), replacing, combining, or improving existing conventional viral inactivation methods. Conventional methods for viral inactivation, such as chlorine disinfection, do not have an effective disinfection ability against viruses (Ashraf et al. 2013). Unlike those methods, NTPs can deal with both

Table 1 Not exhaustive list on types of viruses and their effects on human health

Type of virus	Effects on human health	Ref
SARS-CoV-2	SARS-CoV-2 does not damage only the respiratory system and lungs; it can infect the urogenital system, nervous system, digestive system, and circulatory system. It can also cause an inflammatory cascade. Among its symptoms are mild disease, severe lung injury, and multi-organ failure leading to death, especially in older patients with other comorbidities. Other significant outcomes of coronavirus infection are acute respiratory distress syndrome and pulmonary fibrosis. The infection's long-term implications on human health are unknown, like the virus's possible impacts on cellular lifetime as well as organismal healthspan, which can cause diseases such as Parkinson's and other neurodegenerative illnesses	(Day et al. 2020; Liang et al. 2020; Lippi et al. 2020; Monteil et al. 2020; Zhang et al. 2020)
Rhinoviruses	The main site of RV infection is the nasal mucosa. It is a common cause of colds (acute nasopharyngitis), which is a mild disease of the upper respiratory tract. It can also cause chronic obstructive pulmonary disease, asthma, or cystic fibrosis might become life-threatening	(Myatt et al. 2004; Turner 2007; Ashraf et al. 2013; Blaas and Fuchs 2016; Thibaut et al. 2016; To Kelvin et al. 2017)
MS2 Bacteriophage	MS2 is an enteric virus; it is non-hazardous to humans and animals and is widely utilized as a surrogate for pathogenic viruses in aerosol investigations. It is an example of noroviruses which are highly infectious and are associated with sporadic gastroenteritis	(Olson et al. 2004; Dawson et al. 2005; Tung-Thompson et al. 2015)
Influenza viruses (types A, B, C)	Influenza is a highly contagious viral respiratory disease. A dry cough, headaches, muscular and joint discomfort, and general weariness are among the symptoms. The flu can become dangerous, requiring hospitalization or even death	(Hayden et al. 1998; Brankston et al. 2007; Carrat et al. 2008; World Health Organization 2019)
Varicella viruses	Varicella virus, one of the five human herpes viruses, causes two distinct diseases, varicella (chickenpox) and shingles (herpes zoster). Its symptoms are fever concurrent with a self-limiting rash on the skin and sometimes mucosa. Headache, malaise, and loss of appetite	(Mueller et al. 2008; Andrei and Snoeck 2013; Sauerbrei 2016)
Measles virus	Measles is a disease that can infect only humans; it attacks immunological cells, leading to a rapid deterioration of the immune system. It can cause three different types of encephalitis or central nervous system (CNS) diseases which are acute postinfectious encephalitis, acute progressive infectious encephalitis, and the lethal neurodegenerative disease subacute sclerosing panencephalitis	(Bellini et al. 1994; Norrby and Kristensson 1997; Mrkic et al. 1998; Reuter and Schneider-Schaulies 2010; Mina et al. 2019)
Hantavirus	Hantavirus pulmonary syndrome is a zoonotic disease; its transmission to humans can lead to hemorrhagic fever with renal syndrome or nephropathy epidemic named hantavirus pulmonary syndrome, also leading to disease with severe cardiopulmonary	(Khaiboullina and St. Jeor 2002; Muranyi et al. 2005; Bartholomeusz and Locarnini 2006; Tersago et al. 2009, 2011; Muylaert et al. 2019)
Viral meningitis	Meningitis is considered a bacterial and viral disease. Viral meningitis can infect the human brain, and its infection can cause headaches, encephalitis, malaise, long-term sleep disorders, and depression. In most cases, there are no major side effects	(Peate 1999; Schmidt et al. 2006; Tuppeny 2013; McGill et al. 2017)
Mumps virus	Mumps is a mildly infectious disease that affects children. However, in some situations, its systemic infection can have serious clinical effects, particularly when the sickness is postponed into adulthood. It infects pancreatic Beta cells, which can lead to fever, swelling of the parotid glands, fatigue, low-grade fever, attacks of tachycardia, and night sweating	(Parkkonen et al. 1992; Gut et al. 1995; Nöjd et al. 2001; Mühlemann 2004)

transport and infectivity of airborne viruses by filtration and interact with interactive plasma species (Xia et al. 2019).

Parameters controlling viruses' inactivation performance

Several parameters remain essential in the non-thermal discharge viruses' inactivation, such as virus concentration, input power, air humidity, air composition, reactor design, and type of discharge. It is also worth noting the oxygen concentration.

The effect of the viruses' concentration

The virus concentration effect in the non-thermal discharge viruses' inactivation was reported in several studies (Chen et al. 2010). Indeed, Puligundla and Mok (Puligundla and Mok, 2016) revealed a reduction of at least 4 to 6 log10 of two bacteriophages at concentrations of 10^6 PFU/mL^{-1} after 10 min of exposure to NTP.

After a couple of seconds of discharge treatment, the number of infectious phages decreased quickly, and 6 orders of magnitude inactivation were achieved. On the other hand, the virus concentrations used in NTPs ranked from 1×10^6 PFU mL^{-1} to 300 PFU mL^{-1} within several studies (Chen et al. 2010; Puligundla and Mok 2016; Jiang et al. 2017; Filipić et al. 2020a). We noted 10^5 $TCID_{50}$/mL of bacteriophage MS2, matching 69×10^6 PFU/mL according to Xia et al. (Xia et al. 2019) study, while that of Venezia et al. (Alshraiedeh et al. 2013) denoted 10^9 PFU/mL.

Thus, some works reported a proportional relationship between virus concentration and the inactivation performance with non-thermal plasma: the inactivation yield of virus decrease with very polluted indoor air. This finding might be due to the higher virus concentration, and the step limitation is the reaction between reactive species and viruses (Lee et al. 2021).

Input power

Input power is an important factor in influencing virus removal in NTP reactors. In fact, virus elimination measurements are a function of input power (Mustafa et al. 2018). Several previous studies demonstrated that the removal efficiencies of harmful airborne components increase with the NTP input power (Shimizu and Oda 1999; An et al. 2011; Pinard et al, 2019; Xia et al. 2019). It is well known that the power of the plasma is proportional to the voltage applied in the discharge zone. Indeed, the increase in electric power pleads in favor of having an increase in electric current in the vicinity of the virus. Since the virus is in direct contact with the plasma, the exposure of the virus to species produced by short-lived plasma, including electrons, ions, radicals, and UV rays, is significantly higher compared to other treatment modalities. Likewise, the virus will also be subjected to high electric fields at the plasma-surface interface. All of these active species (OH°, O°, O_3, e^-) ensure the inactivation of the virus (Mohamed et al. 2021).

Indeed, Xia et al. (Xia et al. 2019) examined viruses' inactivation through NTP coupled with a packed-bed dielectric barrier discharge plasma. After NTP treatment, the results revealed a higher inactivation of phage MS2 with a rise in the applied voltage up to 30 kV (Alshraiedeh et al. 2013).

Air humidity

The non-thermal discharge viruses' inactivation can be affected by many environmental factors such as air humidity versus the different reactors. For instance, Cutler et al. (Cutler et al. 2012) demonstrated that for any temperature, the rate of the inactivation of the airborne porcine reproductive and respiratory syndrome (PRRS) was highest at a relative humidity between 25 and 79% and lowest at relative humidity > 80%. Likewise, Xia et al. (Xia et al. 2020) found 98.6% as the PRRSv inactivation efficiency with 38% of relative humidity under 20-kV voltage supplied to the packed-bed NTP reactor. However, some authors investigated the spread of relative humidity (RH) within the NTP reactor, and they found that the RH evolved to reach 60% at a steady state in 30 min (Xia et al. 2019). This result obtained with the NTP reactor corroborates that of Cutler et al. (Cutler et al. 2012) in the case of the PRRS virus, regarding the RH effect on the reactor efficiency. On the other hand, other studies have reported that the relative humidity of the PRRS virus depends on the viral envelopes (Elazhary and Derbyshire, 1979). Viruses with lipoprotein envelopes tend to be more stable at lower relative humidity and non-enveloped viruses more stable at higher relative humidity. Overall, relative humidity plays an important role in the different reactors' yields. The divergence in the resulting level is due to the difference in generating the plasma process, the residence time, reactor configuration, etc.

Reactor for the inactivation of viral aerosols

Over the past 20 years, several technologies have been devised for the inactivation of non-thermal discharge viruses (Jacobs et al. 2010; Alshraiedeh et al. 2013; Sakudo et al. 2014).

Recently, some studies examined microbial inactivation, sterilization, and disinfection using APNTP within a field of biomedical application (Fridman et al. 2008). APNTP applying possesses potential favor over standard chemical

sterilants and disinfectants (Fig. 1). These include the design's simplicity and operation. It uses non-toxic gases with the absence of toxic residues and the production of a large amount of various microbicidal active species, including chemically reactive species (Yardimci and Setlow, 2010; Nayak et al. 2018) (Table 2).

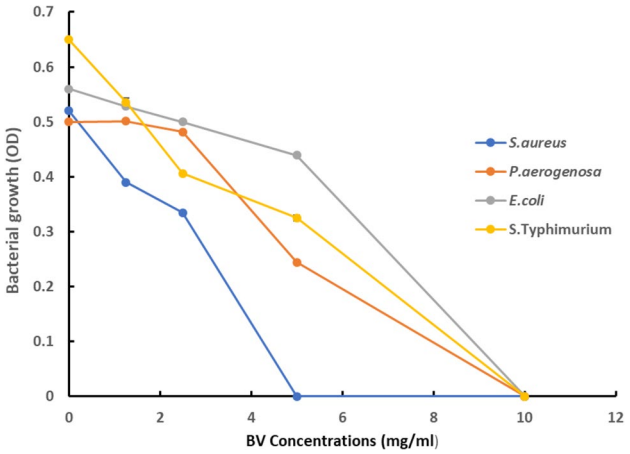

Fig. 1 Schematic of the DBD packed-bed reactor for the inactivation of viral aerosols (Michielsen et al. 2017; Uytdenhouwen et al. 2018)

Combined system for virus disinfection

Several works have been reported on conventional techniques for viruses and bacterial inactivation treatment, whether physical or chemical (Table 3). Some technologies have been combined with different forms of electric discharge plasma or other decontamination processes to deal with various pathogenic microorganisms' high levels of contamination to improve inactivation efficiency (Bourke et al. 2018; Kordová et al. 2018; Rtimi and Kiwi, 2021).

In recent years, current trends have been moving towards the coupling of plasma and nanomaterials with dimensions in the order of a nanometer (i.e., 1 to 100 nm). This process has been well confirmed with the inactivation effects of nanomaterials on various viruses due to a large specific surface area, including the generation of ROS (Abidi et al.

Table 2 plasma reactor configuration for viruses and bacterial inactivation treatment for some types of the virus with reactive species.

Virus	Reactive species responsible for the inactivation	NTP reactor configuration	Mode of inactivation	References
SARS-CoV-2	RONS	Cylindrical cold atmospheric plasma reactor (CCAPR)	DNA/RNA degradation	(Chen et al. 2020)
MS2 bacteriophage	O	Tubular atmospheric pressure cold plasma (TAPCP)	Both protein and DNA/RNA degradation	(Wu et al. 2015)
	O_3		NA	(Xia et al. 2019)
Adenovirus	H_2O_2	surface micro-discharge (SMD) plasma electrode using an insulator plate made of Al2O3	DNA/RNA degradation	(Sakudo et al. 2016)
	O_3		NA	(Zimmermann et al. 2011)
T4, Φ174, and MS2	O_2, NO_2, and $ONOO^-$	Mesh electrode with a planar configuration	Both protein and DNA/RNA degradation	(Guo et al. 2018)
Feline calicivirus (FCV)	O and ONOOH	Tubular reactor plasma	Protein degradation	(Aboubakr et al. 2016)
	O_2 and $ONOO^-$		DNA/RNA degradation	(Yamashiro et al. 2018)
	O_2 and O_3		Both protein and RNA degradation	(Aboubakr et al. 2018)
	NO_x and O_3		NA	(Nayak et al. 2018)
Respiratory syncytial virus (RSV)	H_2O_2	Tubular NTP reactor	DNA/RNA degradation	(Sakudo et al. 2017)
HIV-1	O_2^+, O, NO, and N_2	Cylindrical cold atmospheric plasma reactor (CCAPR)	DNA/RNA degradation	(Volotskova et al. 2016)
Newcastle disease virus (NDV)	H_2O_2, $OH^•$, and NO_x	Magnetically rotated gliding arc & DBD plasma planar reactor	Both protein and DNA/RNA degradation	(Su et al. 2018)
	RONS		RNA degradation	(Schiappacasse et al. 2020)
Influenza viruses	H_2O_2		Both protein and RNA degradation	(Sakudo et al. 2014)
Influenza A	OH and O_3		NA	(Gallagher et al. 2004)

Table 3 Summary of studies on plasma combination technologies for virus inactivation

Combination systems	Virus types	Experimental conditions	Results	Ref
Non-thermal plasma-activated by NaCl or H_2O_2 solutions	Newcastle disease virus (NDV)	10 mL sterile distilled water, 0.9% NaCl, and 0.3% H_2O_2 solutions	Complete inactivation of NDV after only 30 min of treatment	(Su et al. 2018)
Atmospheric pressure non-thermal plasma (NTP) jet with $Ar/O_2/N_2$	Newcastle disease virus (NDV) strain and H_9N_2 avian influenza virus (AIV)	A mixture containing 88% Ar, 2% O_2, and 10% N_2 at a flow rate of 5 L/min was used as working gas	Complete inactivation in 2 min of treatment for both NDV and AIV	(Wang et al. 2016)
Cold oxygen plasma + an internal classic UV-C lamp	Respiratory syncytial virus (RSV) and human parainfluenza virus type 3 (hPIV-3), and influenza virus A (H_3N_2)	50 mL of viral pellets were suspended in PBS	More than 99.98 of reduction regardless of the virus type	(Assadi et al. 2015)
Non-thermal plasma coupled to a packed-bed dielectric barrier discharge reactor	Aerosols of phage MS2	At 30 kV and an airflow rate of 170 standard liters per minute	A reduction of ~ 2 log of the MS2 inactivated and ~ 0.35 log physically removed in the packed bed was observed	(Xia et al. 2020)
Packed-bed dielectric barrier discharge non-thermal plasma combined with filtration	Porcine reproductive and respiratory syndrome virus (PRRSv	From 12 to 30 kV with RH = 38–49% at 5–12 cfm	More than 40% at 12 cfm and more than 80% at 5 cfm of reduction regardless of the virus SARS (MS2)	(Xia et al. 2019)

2019, 2020). The effects resulting from the combination between the plasma in the catalytic oxidation, the photothermal influences, and the release of metal ions allow having a synergistic impact on the antiviral performances (Li et al. 2021). Therefore, there is a comprehensive promise in developing antiviral nanomaterials and using them to air purifier filters, building ventilation systems, antiviral fabrics, and antiviral spray agents, which assists in controlling the spread of viruses through aerosols.

Mechanism of viral inactivation by the non-thermal discharge

Non-thermal plasma constitutes one of the recent processes of advanced oxidation processes (AOPs). This technology allows the formation of heavy mixtures and lighting from the excitation of gases by electric discharge. Probably, the effectiveness of NTPs is because they combine both physical and chemical mechanisms (Ateia et al. 2020). However, these coupled techniques generate highly reactive oxidizing components, free radicals, and ions (e.g., ozone, hydrogen peroxide, hydroxyl, and superoxide radicals) in aqueous solutions under UV irradiation (Wang et al. 2018). Figure 1 shows a schematic of the action of NTP of viral inactivation by the non-thermal discharge. The generation of reactive oxygen species (ROS) and/or reactive nitrogen species (RNS) is the main feature of NTP that contributes to virus inactivation. The main target of ROS/RNS is virus capsid, genome, protein, and glycoprotein. The short lifespan of ROS or RNS makes the identification and assessment of ROS/RNS a challenging task. Furthermore, the experimental conditions (the gas used for the NTP generation, the matrix, the virus treated…etc.) play a crucial role in the generation of particular ROS/RNS.

The most crucial component for evaluating virus inactivation is the degradation of the capsid. The viral envelope or capsid is the first contact point with the host cell. For an efficient recognition of a virus by the cell receptors, their outer structure must be intact.

The increased oxidative force of NTP can denature the virus and genome structure by affecting both proteins and nucleic acids. Conformational disruption of the capsid proteins caused by ROS/RNS can result in loss of viral infectivity due to the virus's disruption binding to receptors on the host cell membrane (Filipić et al. 2020b).

In addition to capsid and nucleic acid, further damage could be seen in lipid components from the envelope the virus influenza A (Sakudo et al. 2014). Particularly in the case of bacteriophage λ (Yasuda et al. 2010) and FCV (Aboubakr et al. 2018), it has been proved that the main mode of NCP inactivation is the degradation of the capsid proteins proceeding with the degradation of nucleic acids (Fig. 2). However, in several

studies, it was impossible to determine which degradation path contributed more to the decay in viral infectivity (Filipić et al. 2020b).

Chemical processes' reactions

It is worthy to note that in humid air, electrons with very high kinetic energy and could react with water vapor to occur reactive species. Then, some reactive chemical species (i.e., H_2O_2, O_3, $O_2^{-\cdot}$, $^{\cdot}OH$) also react by attacking the high-energy electron (Wang et al. 2018). In fact, electrons energy generated through the electrical discharge plasma process can outdo the decay or ionization energy of water molecules (Joshi et al. 1995; Wang et al. 2008). Through electron collisions, the dissociation of water molecules in the air could form H, OH, and other hydrated cations as follows (Hong and Zeng, 2002; Wang et al. 2008):

$$e^{-*} + H_2O \rightarrow OH + H + e \quad (1)$$

$$e^{-*} + H_2O \rightarrow H_2O^+ + 2e^- \quad (2)$$

$$H_2O^+ + H_2O \rightarrow H_3O^+ + OH \quad (3)$$

where * denoted high-energy electron state. These formed radicals could react together or recombine with other reactive species, as presented in the following reactions (Zhou et al. 2016):

$$H + H \rightarrow H_2 \quad (4)$$

$$OH + OH \rightarrow H_2O_2 \quad (5)$$

$$OH + H \rightarrow H_2O \quad (6)$$

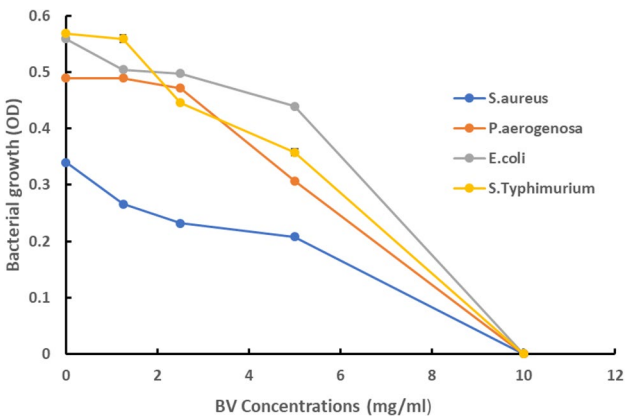

Fig. 2 A schematic of the action of NTP of viral inactivation by the non-thermal discharge

$$e^- + H_2O_2 \rightarrow OH + OH^- \quad (7)$$

$$O_2 + e^- \rightarrow e^- + 2O \quad (8)$$

Despite the free radicals' generation for virus degradation in NTPs, ozone (O_3) reactions also occur. Once $^{\cdot}O$ is formed (i.e., Eq. 8) via high-energy electronic attack, it could react with O_2 and organic matter (M) to generate O_3, as shown in the reaction (9) (Wang et al. 2018).

$$O + O_2 + M \rightarrow O_3 + M \quad (9)$$

where M is organic matter, O_3 could react with various compounds through direct O_3 and indirect O_3 oxidation reactions. In previous studies, also it was found that the ozone produced by plasma was not the main contributor to the inactivation effect; nevertheless, it is involved in the inactivation (Morrison et al. 2021). In fact, Morisson and her co-workers (Morisson et al. 2021) showed that ozone disinfection had demonstrated high efficacy against enveloped and non-enveloped viruses, including viruses similar in morphology to SARS-CoV-2.

Physical processes' reactions

The physical processes of the inactivation effect in non-thermal plasma can occur via UV irradiation (Sun et al. 2005; Wang et al. 2006; Tang et al. 2018), shock waves (Šunka 2001; Ghernaout and Elboughdiri, 2020), and electric field effects (Schoenbach et al. 1997, 2000). Indeed, the UV irradiation from gas-phase discharges is weaker than that from the liquid phase. The types of UV irradiation from gas-phase discharges at atmospheric pressure are generally within the UVA and UVB regions, with wavelengths ranging of 320–400 nm and 280–320 nm, respectively. Matsumoto et al. (Matsumoto et al. 1992) reported that UV irradiation performed an essential part in bacteria inactivation. Moreover, UV irradiation has also been used in the gas-phase discharge plasma process (Xue et al. 2008).

In the absence of electric discharge, the electric field is an alternative method for inactivating cells and processing food products. Previous research reported that a potent electric field could inactivate the microorganisms and biofilm bacteria on the walls of cooling and drinking water pipes (Schoenbach et al. 2000).

Conclusions and outlook

Over the past decades, interest in applying non-thermal plasma technology for virus inactivation within indoor air has considerably increased. In this review paper, commonly used non-thermal plasma reactors and their effectiveness in virus inactivation have been extensively exhibited. Moreover, the inactivation mechanisms and the factors controlling these reactors, such as virus concentration, input power, air humidity, air composition, and reactor design, have also earned attention.

Notwithstanding the determining factors in non-thermal plasma processes, the production and evolution of active species and the physical effects of viral inactivation must be further investigated to explain the mechanisms of plasma oxidation and optimize the oxidation non-thermal plasmas process. Furthermore, investigations should be performed on the impact of target properties, including volatility, hydrophobic/hydrophilic nature, stability, and diffusivity. However, non-thermal plasma can be combined with other technologies involving catalysts like carbonaceous materials, metal oxides, and metal ions. The mechanism of interaction between viral inactivation and catalysts needs to be well studied. Well-mastered non-thermal plasma could be a promising alternative to face these waves of COVID-19 infections.

Author contribution Imen ASSADI: validation, investigation, visualization, resources, writing–original draft, writing–review & editing.

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Declarations

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