Title
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Journal
Plasma processes and polymers (Print), 19(9)

ISSN
1612-8850

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Publication Date
2022-09-01

DOI
10.1002/ppap.202200012

Peer reviewed

Received: 19 January 2022 | Revised: 11 March 2022 | Accepted: 25 March 2022

DOI: 10.1002/ppap.202200012

REVIEW

PLASMA PROCESSES AND POLYMERS

Cold atmospheric plasma for addressing the COVID-19 pandemic

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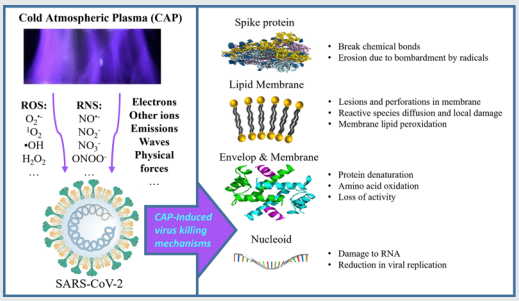
Funding information
U.S. National Institute of Health, Grant/Award Number: Director's Early Independence Award DP5OD028181; Air Force Office of Scientific Research, Grant/Award Numbers: FA9550-14-10317 (UCLA Subaward No. 60796566-114411), FA9550-21-1-0067

Abstract

The coronavirus disease 2019 (COVID-19) pandemic has greatly stressed the global community, exposing vulnerabilities in the supply chains for disinfection materials, personal protective equipment, and medical resources worldwide. Disinfection methods based on cold atmospheric plasma (CAP) technologies offer an intriguing solution to many of these challenges because they are easily deployable and do not require resource-constrained consumables or reagents needed for conventional decontamination practices. CAP technologies have shown great promise for a wide range of medical applications from wound healing and cancer treatment to sterilization methods to mitigate airborne and fomite transfer of viruses. This review engages the broader community of scientists and engineers that wish to help the medical community with the ongoing COVID-19 pandemic by establishing methods to utilize broadly applicable CAP technologies.



KEYWORDS
low temperature plasma (LTP), nonthermal plasma (NTP), plasma virus killing, SARS-CoV-2 plasma disinfection

1 | INTRODUCTION

Over the past year, the world has been shuddered by the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Belonging to the β-coronavirus genus, SARS-CoV-2 is an enveloped positive-sense RNA virus capable of infecting mammals.[1,2] It is the successor to the virus that caused the 2002–2004 SARS outbreak (SARS-CoV-1).[3] As an airborne virus, it can be transmitted in humans through respiratory droplets in a similar way to common colds and the flu.[4] The rapid spread of the virus has quickly reached a pandemic status, threatening nearly the entire global population and leaving millions affected by the clinical manifestations and morbidities associated with the disease it causes, coronavirus disease 2019 (COVID-19).[5–7] Patients with COVID-19 most often exhibit symptoms of common viral respiratory tract infections, such as fever, cough, and pneumonia. In severe cases, the cytokine storm that occurs during an uncontrolled COVID-19-mediated inflammatory response can result in a massive capillary leak and ultimately acute respiratory distress syndrome (ARDS), leading to death. Scientists, engineers, and medical researchers are actively searching for methods to address COVID-19 via the development of preventative strategies that leverage improved understanding of viral transmission mechanisms, new rapid diagnostics, vaccines for primary immunization, and antiviral therapies.[8–13] From a preventative standpoint, while several COVID-19 vaccines are now deployed worldwide, therapeutic discussions to date have primarily focused on how to repurpose different agents that yield antiviral effects by impacting different points of the viral cycle or stem the tide of the massive inflammatory response in severe cases.[14,15] For the most part (and for the average patient) clinical management has been primarily supportive.[16,17] The best approach to address the disease remains the prevention of widespread transmission in the community.[18] This underscores the urgent need to develop effective disease prevention and treatment strategies, particularly for high-risk populations, and to control or curb possible future outbreaks.

Plasma (from the Ancient Greek πλάσμα) was first described in 1922 by the American chemist Irving Langmuir as one of the four fundamental states of matter (i.e., solid, liquid, gas, and plasma).[19] Recent progress in terrestrially generated atmospheric plasma has led to the generation of cold atmospheric plasmas (CAP) with ions/heavy particles close to room temperature that are not subject to local heating.[20–22] There are many categories to classify CAP sources, including plasma discharge mode, interaction characteristics with objects, and excitation frequency. CAP discharge modes include arc discharge (e.g., arc jet, gliding arc, plasma torch, and arc), spark discharge (e.g., corona), and glow discharge (e.g., plasma jet, dielectric barrier discharge [DBD], and microplasma array).[23] Classification according to electrical configuration and plasma/object interaction characteristics provides the general distinction, with various kinds of CAP developed for each. CAP has been utilized for a wide range of applications in biomedical engineering, a use that is rapidly emerging in the field of plasma sciences, as identified by a recent consensus report from the National Academies of Sciences, Engineering, and Medicine.[24] In 1996, Chau et al.[25] employed cold plasma to remove bacteria from material surfaces for the first time. Ten years later, Yonson et al.[26] applied cold plasma to human hepatocytes cells for cancer treatment. In 2010, Isbary et al.[27] carried out 291 treatments in 38 wounds and demonstrated that CAP significantly reduced the bacterial load in treated wounds, regardless of the bacterial species. In addition, Metelmann et al.[28] carried out CAP treatment on 12 patients with advanced squamous cell carcinoma of the head and neck and observed an overall beneficial therapeutic effect. Patients receiving CAP were noted to request less pain medication and a reduction of the typical fetid odor seen in infected wounds with an increased microbial load. CAP has also been applied for skin regeneration by promoting the formation of a layer of intact desiccated epidermis that acts as a natural biologic dressing to promote rapid healing.[29] These studies further demonstrated that CAP is a safe technology that is not chromophore dependent and does not result in significant damage to the epidermis. Multiple reviews cover CAP applications and safety considerations for animal/human living tissue sterilization, dermatology, blood coagulation, wound healing, tissue regeneration, cancers, and other diseases.[30–32]

Mohamed et al.[33] provided an excellent review of CAP as an antiviral strategy and provide insight into its virucidal action, antiviral mechanisms, and potential application value. Notably, plasma-based oxidants and active substances have been shown to initiate viral inactivation and the efficient virucidal properties of CAP. Several groups have investigated this therapeutic effect and the potential virucidal mechanism of CAP.[34-38] Until about 2015, only a few viruses, including MS2 phage, adenovirus, and influenza virus were reported to be responsive to CAP exposure.[39,40] Aboubakr et al.[41] described the effects of CAP on Feline Calicivirus inactivation through chemical analysis and verified two distinctive pathways based on singlet oxygen and

peroxynitric acid. Recent studies have also demonstrated that plasma can degrade SARS-CoV-2 RNA and modify vital viral structures such as spike proteins required for virus intracellular entry.[42,43] Chen et al.[44] found that CAP could kill SARS-CoV-2 on the surface of living organisms within 180 s. Other groups have reported the capability to apply CAP for the inactivation of airborne pathogens.[45-47]

The efficacy of CAP in microbial killing is due to its capability to generate bioactive species, such as electrons, charged particles and molecules, reactive oxygen species (ROS), reactive nitrogen species (RNS), and free radicals, and to control physical phenomena, including electromagnetic fields, physical forces, and electric fields.[48-50] In addition to its potential benefits in infection control and wound healing, CAP has also been applied in studies directed at hemostasis control, treating skin diseases, immunotherapy, and regenerative medicine.[51] Most notably for COVID-19-related applications, CAP has been shown to inactivate viruses through in situ production of ROS and RNS.[41,46,52] Existing decontamination methods such as exposure to ultraviolet (UV) radiation cannot be applied directly to individuals as the durations required to degrade viruses will also damage human skin and other tissues. In contrast, technologies that leverage CAP can not only be implemented for disinfecting contact surfaces (Figure 2) but can also be used for hand sanitization.

2 | CAP-MEDIATED DISINFECTION METHODS FOR COVID-19

2.1 | Gas plasma disinfection

Plasma jets, corona discharges, microwave discharges, and DBDs are common sources of CAP (Figure 1).[33,53,54] Plasma jets, including different configurations, enable gas discharge in an open electrode arrangement and project the plasma's reactive species.[55] Corona discharges are weakly luminous discharges often appearing near sharp electrode geometries (e.g., edges, thin wires, or points) at atmospheric pressure.[56] Microwave-driven discharge plasmas are generated by magnetrons to generate electromagnetic waves that transmit energy to excite the plasma electrons.[57] DBDs are generated between two electrodes that are typically separated by at least one dielectric layer.[58] Plasma jets and DBDs are widely used to generate CAP as the dielectric material between the electrodes prevents the transition to an arc and limits the discharge current through the electrodes. These plasma sources are operated in the air and often use seed gases to facilitate plasma generation. For example, noble gases such as argon (Ar) and helium (He) are widely used as seed gases to assist in CAP generation and typically exhibit a stable generation of glow discharges with low gas temperatures. Other plasma sources convert just the ambient air (or surrounding gas) in close vicinity to the target surface into plasma.[59]

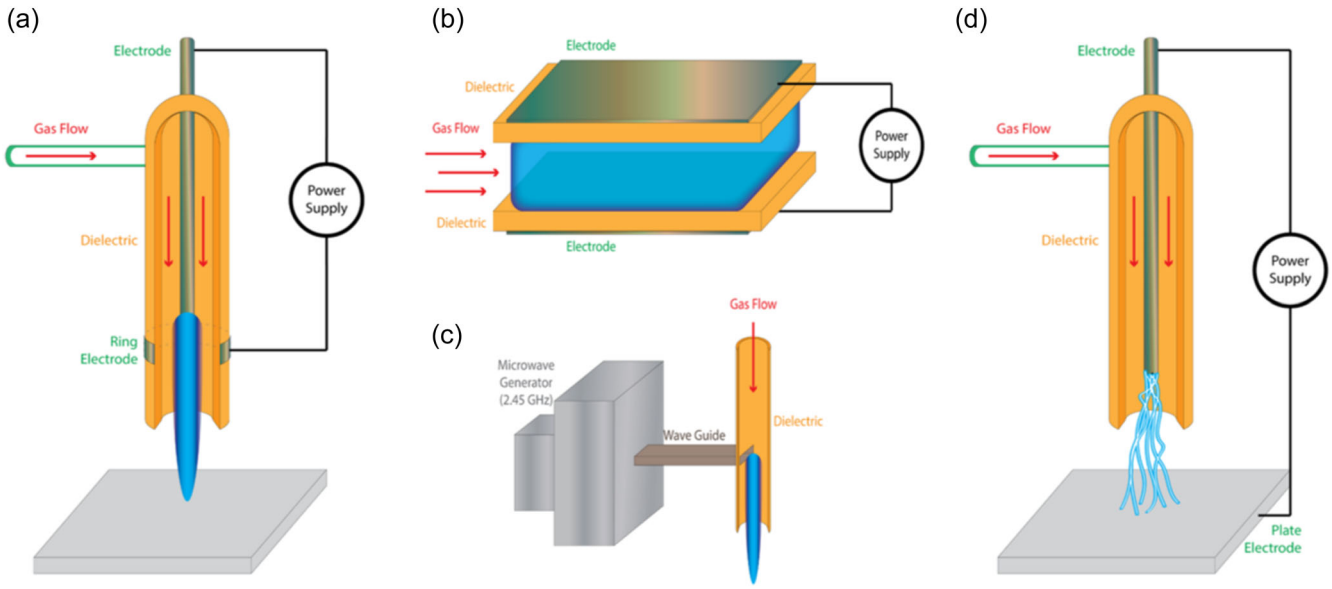


FIGURE 1 Typical cold plasma system configurations: (a) plasma jet, (b) dielectric barrier discharges, (c) microwave discharge, and (d) corona discharges. Reproduced from Reference [53]

CAP sources can be classified with regard to excitation frequency due to their influence on the behavior of electrons and ions. Except for microwave sources, two groups are commonly used: (1) radio frequency (RF) wave sources and (2) direct current (DC) and low-frequency sources.[60] For RF-driven sources, CAP can be generated at either low or high power, which affects the properties of the plasma. Types of RF-driven devices include coupled CAP jet, plasma torch, microplasma, and cold plasma torch.[61] As a typical example, Cheng et al.[62] developed an AC-driven plasma jet operating at 30 kHz and voltage up to 10 kV. Plume length was dependent on the voltage, frequency, and flow rate of the feeding gas, which was either He or a He/O_2 mix at 2–6 L/min. Low-frequency DC sources can work in either pulsed or continuous modes. A pulsed power supply for plasma discharge is technically more complex than a continuous DC plasma source, potentially compromising reproducibility. However, pulsed mode enables operation at high power levels, but lower time-averaged energies to reduce thermal stress on the device. Deng et al.[63] presented a DBD consisting of a dielectric tube wrapped with a metallic strip as the powered electrode and a sample holder as the ground electrode placed 10 mm from the dielectric tube. The DBD was sustained by a peak voltage of 8 kV with a frequency of 30 kHz and employed He at a flow rate of 5 slm alone or mixed with 25 sccm of O_2. A review of several biomedical CAP device configurations is provided by Lu et al.[64]

Our group has demonstrated that CAP sources such as plasma jets and DBD plasma can kill viruses effectively.[44] Generally, DBDs are suitable for sterilizing larger areas, while plasma jets are appropriate for disinfecting small and complex surfaces. The plasma jet shown in Figure 2a uses Ar as a seed gas, which improves the jet density compared with He. The optical emission spectroscopy (OES) spectrum of the Ar plasma jet is shown in Figure 2a.[44] A high density OH peak was detected at 309 nm and a low-density O peak was identified at 777 nm. Peaks corresponding to the low-intensity N_2 second-positive system ($C^3\Pi_u - B^3\Pi_g$) at 337, 358, and 381 nm were also present. In addition, Ar bending modes in the range of 650 nm and 850 nm were observed. Interestingly, SARS-CoV-2-infected Vero-E6 cells exhibit a strong viral cytopathic effect, indicated by structural changes observed in the host cells (Figure 2b). The absence of a cytopathic effect indicates no active virus. Data presented in Figure 2c demonstrate that Ar-fed CAP treatment can effectively inactivate SARS-CoV-2 on the surfaces of six commonly handled materials (e.g., plastic, metal, cardboard, basketball composite leather, football leather, and baseball leather) for durations ranging from less than 30 s to less than 180 s. Metal and plastic surfaces were decontaminated by 30 s of exposure, showing CAP treatments under 30 s are needed for a wide range of surfaces. These data also indicate that ROS and RNS concentration plays a major role in SARS-CoV-2 inactivation. Consumables such as alcohol or 1%–3% H_2O_2 also effectively inactivate virions such as SARS-CoV-2. Therefore, the primary advantage of CAP-based treatments, such as direct exposure of CAP or plasma-activated water to a surface, is that they are easily and economically obtained from air/water and electricity without the expense and logistics of maintaining supplies and supplies lines for consumables. Given cost and supply chain limitations, one may consider not using seed gases such as argon. Alternatively, CAP devices operated with an air feed are able to present higher concentrations of ROS than Ar-seeded CAP. [65] For example, Bisag et al.[42] employed air plasma to inactivate bioaerosol containing *Staphylococcus epidermidis* and purify SARS-CoV-2 RNA suspensions as a potential technology to prevent airborne indoor transmission.

Airborne respiratory droplets containing SARS-CoV-2 virions emitted by infected patients are the primary source of infection and environmental contamination. Thus, to control COVID-19 effectively, it is important to determine the time SARS-CoV-2 virions maintain infectivity in the air and on surfaces, as well as to investigate the chemical/physical methods that reduce the infectivity (Figure 2a).[53] Bisag et al.[66] investigated the effect of CAP on aerosolized SARS-CoV-2 viral particles (Figure 3). No residual viral RNA was detected and the structural integrity of the target gene sequences was destroyed. These results provide evidence that CAP can inactivate bioaerosols to reduce the spread of COVID-19. Ibanez-Cervantes et al. studied the disinfection of N95 masks contaminated with either SARS-CoV-2 or *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa*, and *Enterobacter* (ESKAPE) bacterial species by employing H_2O_2 plasma.[54] No SARS-CoV-2 was detected in all assays employing five different virus concentrations, and *A. baumannii*/*S. aureus* could not be cultured with inoculums of 10^2–10^6 CFU after treating N95 masks with H_2O_2 plasma. Disinfection of N95 masks by utilizing the H_2O_2 plasma technology is, therefore, a method to enable N95 mask reuse.

CAP-based approaches for addressing COVID-19 contribute to viral elimination of SARS-CoV-2 via multiple methods, including etching of the spike protein, damage to lipid membranes comprising the viral envelope, denaturation of envelope/membrane proteins, and/or destruction of genetic materials (Figure 4). CAP

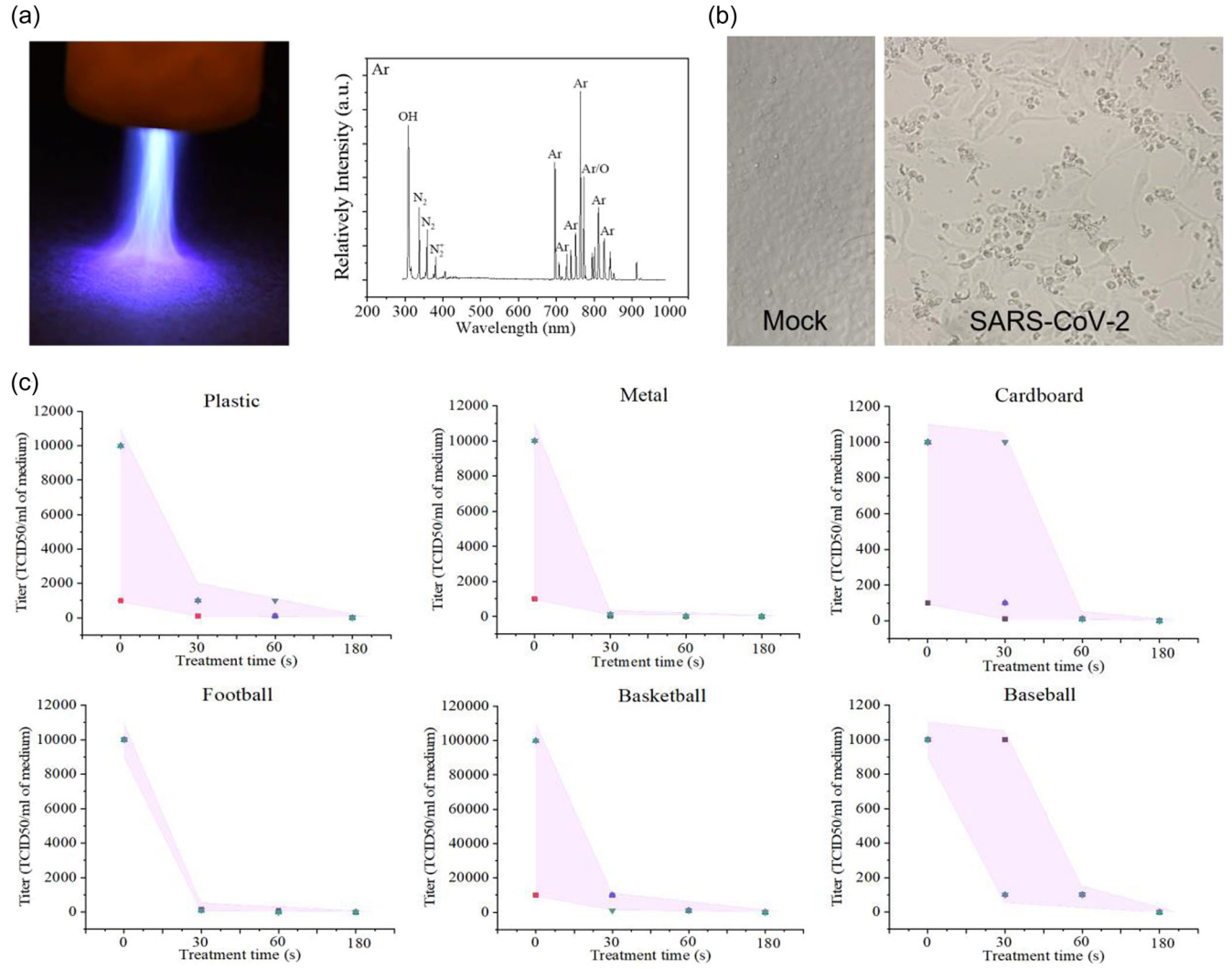


FIGURE 2 Argon (Ar)-fed CAP disinfecting SARS-CoV-2. (a) Ar-fed CAP treatment of a plastic surface and the optical emission spectrum of reactive oxygen and nitrogen species (exposure: 250 ms). (b) Bright-field image of SARS-CoV-2-infected Vero-E6 cells showing a viral cytopathic effect (CPE) following exposure to CAP. Uninfected (i.e., Mock) cells are included as a negative control (scale bar: um). (c) SARS-CoV-2 titer response to CAP treatment times of 0, 30, 60, and 180 s on surfaces of plastic, metal, cardboard, leather football, composite leather basketball, and leather baseball. The distance between the plasma device and the surface is approximately 15 mm. The standard error bar in each graph is shown as a shaded area. Reproduced from Reference [44]

has been shown both in vitro and in vivo to be effective against a wide range of microbes due primarily to interactions with ROS and RNS products generated by the plasma.[67,68] SARS-CoV-2 is a positive-sense single-stranded RNA virus and is similar to other coronaviruses to the extent that it should respond to CAP treatments.[69,70] The application of CAP for killing viruses relies on plasma-generated reactive species that induce disruption of the viral envelope and capsid and loss of infectivity. The levels of these reactive species can be adjusted by plasma source design, the type of feeding gas used, operating conditions, the nature of the product/substrate, and the microorganism itself. Previous studies have demonstrated the ability to break structurally important bonds in a variety of biological systems, such as C–C, C–O, and C–N.[71,72] Using molecular dynamic (MD) simulations Attri et al.[43] observed that the C-terminal domain of SARS-CoV-2 spike (S) protein became unstable after plasma oxidation, decreasing the binding free energy of this vital viral structure. Further, intracellular pH may be lowered by CAP-generated ROS and RNS, disrupting viral replication due to the alteration of the local homeostatic environment.[58] Charged particles accumulating on viral structures may also lead to damage through electrostatic disruption.[73] The electrostatic forces from such an accumulation can exceed the tensile strength of viral envelope membranes, leading to rupture. ROS, such as OH radicals and $^1O_2$,

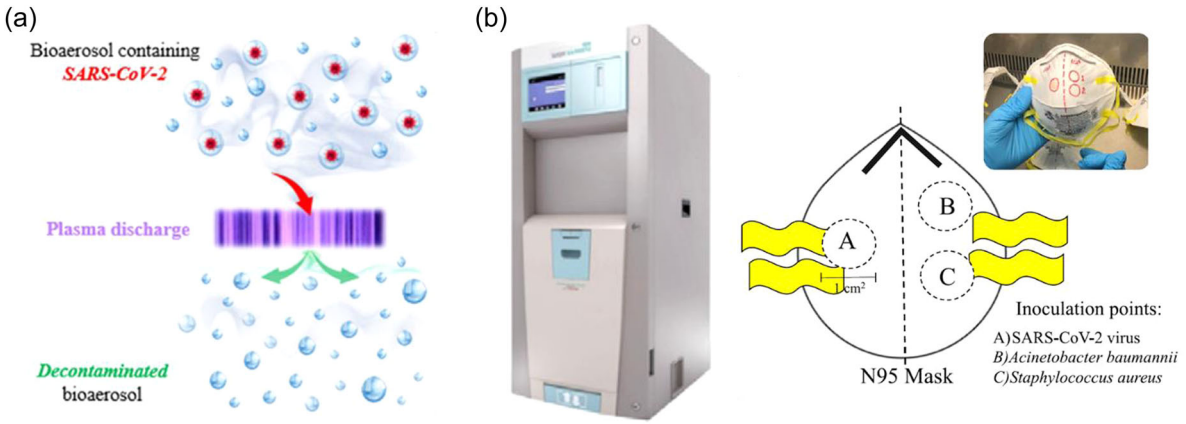


FIGURE 3 Gas plasma disinfection. (a) Dielectric barrier discharge plasma source is used to inactivate suitably produced bioaerosols containing *Staphylococcus epidermidis* or purified SARS-CoV-2 RNA. Reproduced from Reference [66]. (b) Disinfection of N95 masks artificially contaminated with SARS-CoV-2 and *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* (ESKAPE) bacterial species using hydrogen peroxide plasma. Reproduced from Reference [54]

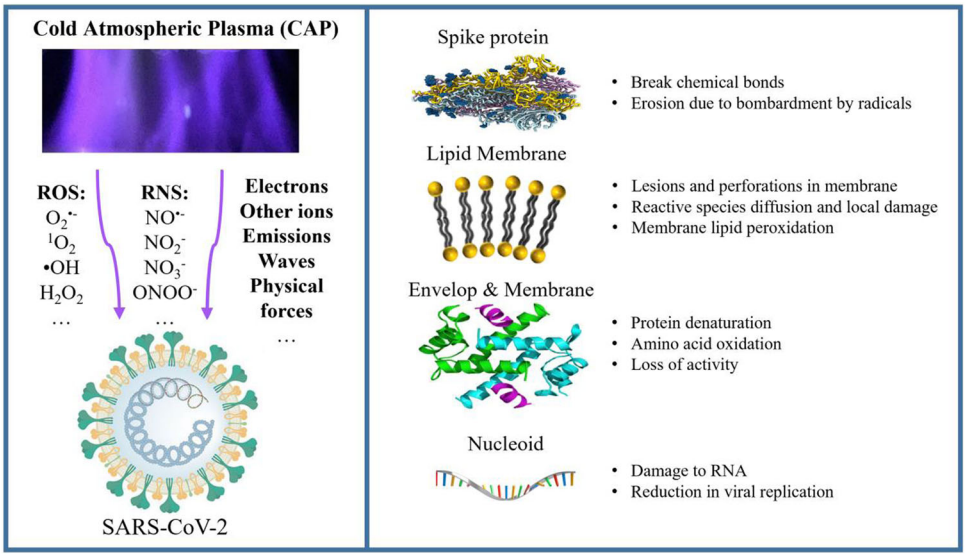


FIGURE 4 Potential mechanisms for the action of cold atmospheric plasma on SARS-CoV-2 include erosion of the spike protein, damage to the viral envelope via peroxidation of lipid membranes, denaturation of critical envelope/membrane proteins, and destruction of genetic materials, which disrupts the virus' structure, function, replication, and lifecycle. RNS, reactive nitrogen species; ROS, reactive oxygen species

also play a part in disrupting viral structures as they can drive protein denaturation and virus inactivation.[74] These reactive species can induce the oxidation of amino acids, nucleic acids, and unsaturated fatty acid peroxides through interaction with viral envelope lipid membranes, changing the lipids' structure and function. In addition, ROS can destroy nucleoid molecules and react with nearby organics to compromise critical viral functions and components.[75] Jin et al.[76] observed that CAP treatment reduced the total RNA concentration of SARS-CoV-2 pseudovirus as well as destroyed viral RNA, suggesting that CAP sterilization affects the virus' RNA polymerases and replication machinery. Azgari et al.[77] investigated several mechanisms contributing to SARS-CoV-2 mutation profiles and inactivation and suggested that ROS, a CAP-produced substance, might be the key element in inducing SARS-CoV-2 G > U substitutions. In addition, several other mechanisms contribute to the antimicrobial effects of CAP, including the generation of other reactive atoms and ions, electrons, metastable, and electronically/vibrationally excited molecules. As discussed earlier, SARS-CoV-2 has been effectively killed

by CAP on a variety of surfaces and should, by the same mechanisms, be extensible to airborne viruses.[44] Therefore, solutions that leverage CAP can pave the way for new and effective means for COVID-19 prevention and control.

2.2 | Plasma-based media for sanitization and infection control

Recently, CAP-activated liquid media has been applied as an antimicrobial agent that represents another important approach in the field of plasma biomedicine (Figure 5a).[78-82] These media efficiently inactivate bacteria and viruses by inducing damage to biological macromolecules. For example, plasma-activated water (PAW) inactivated ϕ174, T4, and MS2 bacteriophages similarly to direct plasma treatment.[79] PAW inactivated ϕ174, T4, and MS2 bacteriophages by damaging the proteins and DNA of bacteriophages. DNA and protein analysis revealed that the reactive species generated by plasma damaged both nucleic acids and proteins, especially singlet oxygen that inactivates different types of bacteriophages in water, including double-stranded DNA, single-stranded DNA, and RNA bacteriophages, by damaging nucleic acids and proteins and causing bacteriophages to aggregate. PAW inactivation resulting from the ROS/RNS stored in the water has the additional advantage of providing precise control of ROS/RNS dosage and uniformity.[83] Leveraging these capabilities, Guo et al.[84] proposed PAW for preventing the infection of pseudoviruses presenting the SARS-CoV-2 S protein as a potent disinfection agent for SARS-CoV-2 (Figure 5b). The short-lived ROS in the PAW, such as $ONOO^-$,

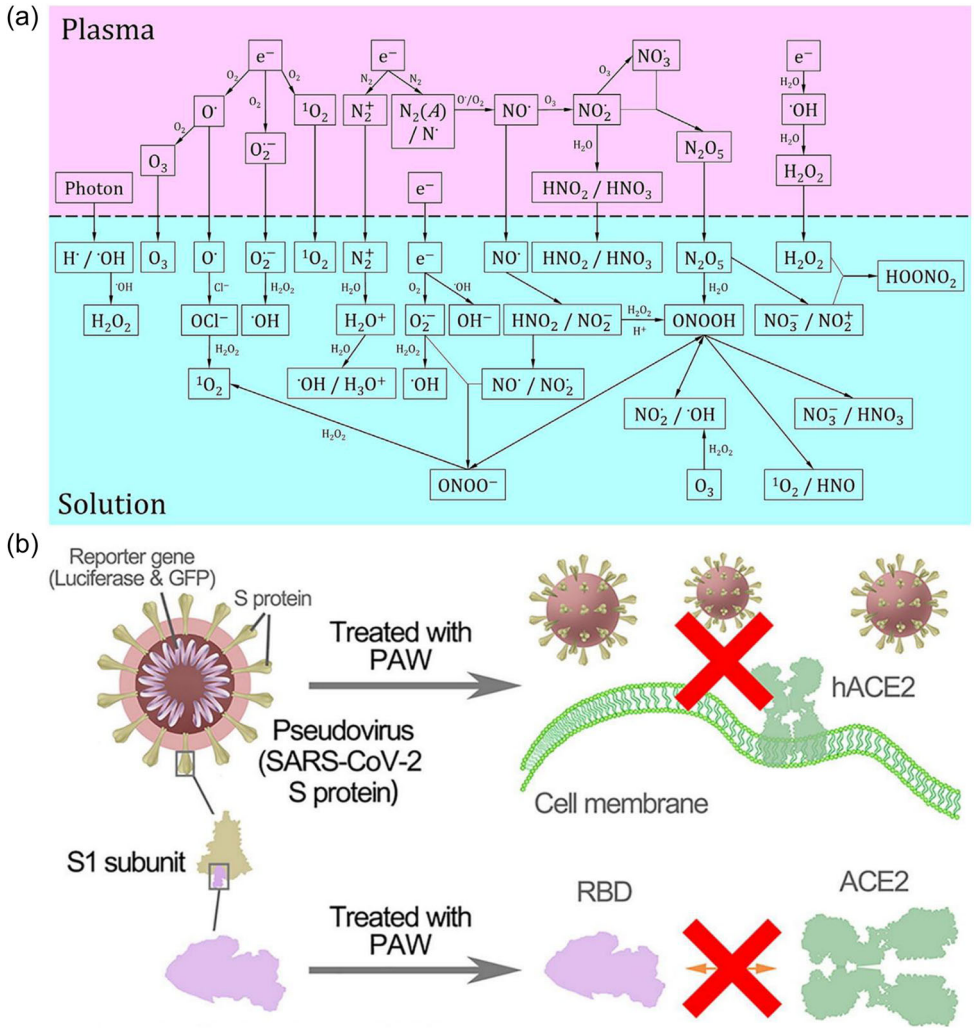


FIGURE 5 Plasma solution disinfection. (a) Schematic of key plasma-generated species relevant to virus inactivation: species both in gas and liquid phases. Reproduced from Reference [33]. (b) Plasma-activated water (PAW) for SARS-CoV-2: treatment with PAW alters the SARS-CoV-2 spike (S) protein receptor-binding domain (RBD), altering its ability to interact with angiotensin-converting enzyme 2 (ACE2). Reproduced from Reference [84]

contribute primarily to SARS-CoV-2 S-protein inactivation. PAW after 30 days and room-temperature storage remained capable of largely disrupting the S protein's receptor-binding domain (RBD) interaction with the angiotensin-converting enzyme 2 (ACE2) receptor.[85] Their findings provide evidence of a potent disinfection strategy to combat the COVID-19 pandemic.

The importance of primary infection control measures, such as proper hygiene, has been highlighted extensively for COVID-19.[86] Cleaning hands frequently with alcohol-based hand sanitizers or soap and water has been cited by the World Health Organization as being "one of the most important hygiene measures in preventing the spread of infection." Our hands are one of the most frequent transmission routes for many infections because they come in frequent and direct contact with known portals of entry for pathogens, such as the mouth, nose, and eyes. Free radicals and reactive species generated in the atmosphere and at the plasma-medium interface can penetrate water interfaces and enter the so-called "bulk medium" to react and/or recombine,[65,87] giving rise to the generation of more stable reactive species such as hydrogen peroxide (H_2O_2)/nitrite (NO_2^-) and decreasing the pH of liquids. According to the Centers for Disease Control, H_2O_2 is a stable and effective disinfectant against viruses.[88] Thus, a CAP-activated medium that generates a high concentration of H_2O_2 may be used as a hand sanitizer to prevent the transmission of SARS-CoV-2. Viral inactivation by CAP-activated media results from the combined action of a low pH and a high positive oxidation–reduction potential.[89] The CAP-activated medium can also kill active SARS-CoV-2 virions on the surfaces of medical PPE, equipment, and instrumentation. Similiar CAP-based reagents will be extremely valuable for sterilizing/disinfecting homes, offices, and public spaces, such as restaurants, bathrooms, hospitals, and laboratories. This technology avoids the need for consumables, such as alcohol-based sanitizers, and is thus not susceptible to limitations in the supply chain.

3 | PLASMA-GENERATED NITRIC OXIDE FOR COVID-19 PATIENTS

Another important component of CAP is nitric oxide (NO).[90] NO is a gas that enables diverse biological activities and can interact with superoxide (O_2^-) to form peroxynitrite ($ONOO^-$), which, in turn, mediates virucidal or cytotoxic reactions.[91] *NB*NO is unstable and reacts with oxygen to form oxides of nitrogen (NO_x).[92] Moreover, NO also plays a major role in regulating airway function and in treating inflammatory airway diseases.[93] The beneficial effects of NO inhalation are observed in many critically ill patients with severe ARDS as it impedes the synthesis of viral proteins and RNA.[94,95] In addition, the organic NO donor S-nitroso-*N*-acetyl penicillamine can remarkably obstruct the replication cycle of SARS-CoV,[96,97] suggesting that NO inhalation may be potentially beneficial for the treatment of COVID-19 patients.[98] NO generation is most prominent for CAP devices that use nitrogen and oxygen mixtures as their feeding gas. Operators can adjust the ratio of the feeding gas mixture, the operating conditions, and other parameters in a nitrogen atmospheric environment to reduce the presence of other oxides of nitrogen (e.g., NO_2). Although patients are able to inhale purified NO without difficulty, it can react with O_2 to form harmful NO_x byproducts in the trachea that can disseminate from the mouth to the lungs. Despite this possibility, NO has proven to be effective and the potential toxicity from increased NO_x species may be outweighed by the emergent need to address potentially devastating COVID-19 symptoms acutely. In a recent case series, Abdollahimajd et al.[99] employed nasal cold plasma for three symptomatic COVID-19 patients and observed that their symptoms and general condition gradually improved. These findings suggest CAP may prove to be a promising source for controllable NO for COVID-19 patients in both emergent and intensive care settings; however, additional investigations are required.

4 | CAP-ENHANCED IMMUNOTHERAPY FOR COVID-19 PATIENTS

To better survive in host cells, viruses such as SARS-CoV-2 employ multiple strategies to avoid immune responses.[101,102] COVID-19-infected patients typically present with severe immune dysfunction and are at high risk of developing cytokine release syndrome, which contributes to a decrease in the number of regulatory T cells and natural killer (NK) cells as well as an increase of inflammatory cytokines such as interleukin 6, an altered CD4/CD8 T-cell ratio, fever, tissue/organ dysfunction, and abnormalities in hemostasis.[103-105] These changes hinder the immune system from mounting an effective adaptive response to the virus.[106,107] Boosting both the function and the number of immune effector cells in COVID-19 patients is crucial for successful recovery. For example, effector T cells play an important role in cell-mediated viral clearance via the activation of $CD8^+$ cytotoxic T cells.[108] Currently, immunomodulation agents are used to counteract the immune dysregulation seen in COVID-19 patients.[109,110] Recently, our group

and others have demonstrated that CAP can be applied similarly to modulate the effects of immunotherapies for several applications in biomedicine.[100,111,112] Figure 6 illustrates how CAP-based treatments can promote dendritic cell (DC) maturation in the lymph node, where DCs can present major histocompatibility complex-peptide epitopes to T cells during primary immunization. The subsequent T cell-mediated immune response can be augmented further via the administration of immune checkpoint inhibitors, resulting in enhanced local and systemic antiviral immunity. These studies show that the application of transdermal plasma may stimulate and prime the immune system for a robust systemic response during immunotherapy. In addition, we could consider CAP potentially as a vaccine against SARS-CoV-2, which is capable of creating a redox environment resembling virus infection, attracting and activating the immune system but sparing the actual infection. Bundscherer et al.[113] investigated the impact of cold plasma treatment on mitogen-activated protein kinase signaling pathways of human immune cell lines and found that CAP is able to stimulate human immune cells by activating both proapoptotic as well as proproliferative signaling cascades in a treatment time-dependent manner. Therefore, by leveraging this capability, CAP can provide a solution for modulating immunotherapies directed at different disease targets, which may offer additional opportunities for improving the treatment of severely ill COVID-19 patients.

5 | SUMMARY AND FUTURE PROSPECTS

Although the trajectory of the ongoing COVID-19 pandemic is difficult to predict, timely development and implementation of effective and reliable countermeasures are needed urgently. CAP-based disinfection methods via direct application or CAP-activated media act by disrupting the integrity of the virus' vital structural and/or functional components and life cycle. These approaches offer several advantages over conventional sterilization methods for SARS-CoV-2. CAP-based technologies can be easily utilized and deployed during infectious disease crises without requiring costly consumables that require robust and uninterrupted supply chains, or expensive and dangerous chemicals. Direct CAP application or CAP-activated media are able to safely and effectively disinfect a wide range of surfaces, including skin and medical PPE, while CAP discharges effectively decontaminate SARS-CoV-2 bioaerosols.

As a potentially effective and antiviral technology, CAP addresses several limitations of traditional antiviral and sterilization methodologies. For example, a drawback of UV-C irradiation is that it must be applied uniformly and directly on exposed surfaces with limited surface penetration and without diffusion and turning functions. Solutions that combined the fluidity of plasma could effectively solve this problem.[114,115]

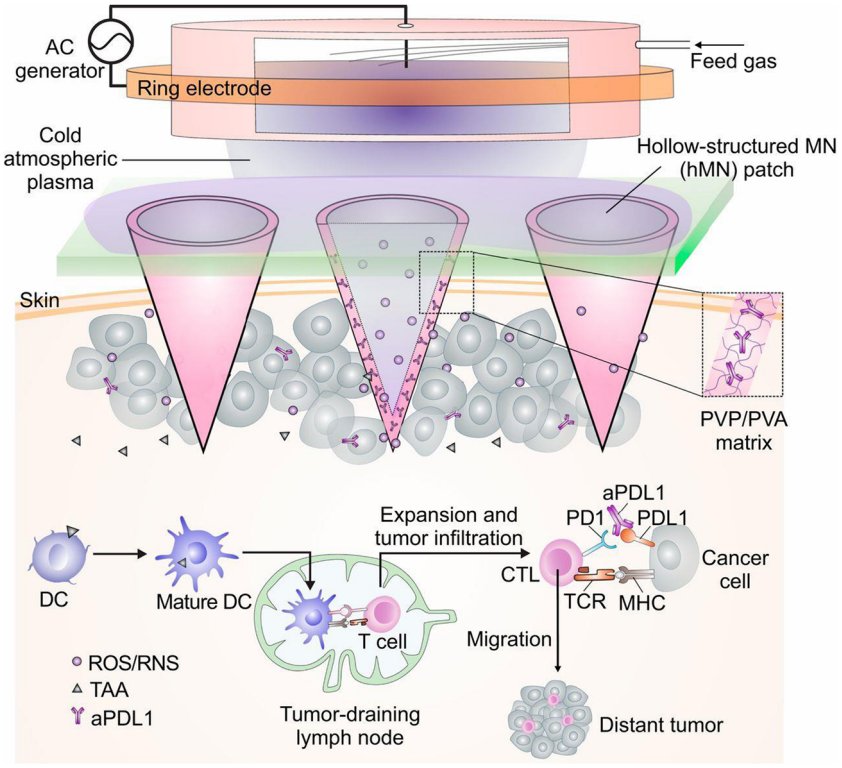


FIGURE 6 Schematic illustrating transdermal plasma-mediated immune checkpoint blockade therapy. Reproduced from Reference [101]. DC, dendritic cells; RNS, reactive nitrogen species; ROS, reactive oxygen species

While the antiviral effect of plasma is independent of the viral subtype and has a wide range of applicability,[116] broader adoptions of CAP technologies face multiple challenges. For example, the ability of CAP to destroy viral particles is reduced by external factors, such as treatment method,[45,117] humidity,[35,118] and the surface material.[44,119] Second, although plasma as a highly ionized gas can penetrate some objects (such as cloth, skin, and tissues), it cannot penetrate the surface of metal, plastic, and glass. Studies have shown that a high-energy electron beam has controllable penetration and has been used to inactivate coronavirus on cold chain food outer packaging.[120] Therefore, if combined with plasma, electron beams could be considered for simultaneous inactivation of viruses both inside and outside objects. In addition, as SARS-CoV-2 is primarily transmitted through air,[121] it is challenging to configure CAP sterilization devices for large spaces with high airflow to meet requirements for sufficient exposure time to achieve effective virus elimination.

Biomedical technologies that leverage CAP also offer unique opportunities to enhance antiviral therapies. Studies have shown that CAP boosts the body's immune response, which can be leveraged to treat viral pathogens in the body rather than relying on the direct application of CAP.[122,123] Combined with current preventive approaches, such as vaccination, plasma could be applied to enhance vaccine delivery and/or conferred immunity.[124-126] Plasma might be employed to enhance viruses' antigenicity in vaccine preparations following inactivation or may be applied to the skin to promote the activity of antigen-presenting cells, enhancing responses to immunotherapies or during immunization.[33] In addition, different manufacturing equipment can generate different types of CAP, making it possible to tailor CAP technologies for specific biomedical scenarios. While the care of COVID-19 patients remains primarily supportive, CAP-based strategies may also be considered for generating inhaled NO for treating critically ill and intubated individuals. Moreover, CAP-enhanced immunotherapies add to the clinical arsenal used to fight COVID-19 by modulating hyperactive immune responses as well as restoring depleted T cell and NK cell numbers, tissue/organ function, and normal hemostasis. Moving forward, an important challenge for the CAP and medical research communities will be to determine the appropriate reactive species and effective delivery methods that enable robust preventative measures for improving infection control and the clinical translation of new treatments for COVID-19 and in consideration of future pandemics. Additionally, CAP and PAW both have several promising biomedical applications. One key advantage of CAP and PAW is that they can be easily obtained from air/water and electricity, offering a cost-effective sterilization solution without the expense and logistics for maintaining expensive and robust supply chains required for conventional approaches that rely on consumables such as alcohol and hydrogen peroxide.

ACKNOWLEDGMENTS

This study was supported by the Air Force Office of Scientific Research grants FA9550-21-1-0067 and FA9550-14-10317 (UCLA Subaward No. 60796566-114411). Steven J. Jonas acknowledges support from the NIH Common Fund/Office of the Director, NIH, through an NIH Director's Early Independence Award under award number DP5OD028181.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this review.

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How to cite this article: Z. Chen, F. Bai, S. J. Jonas, R. E. Wirz, *Plasma Processes Polym*. **2022**, e2200012. https://doi.org/10.1002/ppap.202200012