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REVIEW ARTICLE

Cold Atmospheric Plasma Applications in Viral Inactivation: Systematic Review and Metanalysis

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Abstract
This work is a systematic review conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A predefined protocol was followed to ensure a transparent, reproducible, and methodologically rigorous selection and analysis of the available literature on the use of cold plasma for viral inactivation. Cold atmospheric plasma (CAP) technology has emerged as a promising tool for combating viruses. This study presents a systematic review of current knowledge regarding CAP applications in virology. A comprehensive search was conducted across Scopus and Web of Science databases, including studies published between 2000 and 2024 that explored the use of CAP in virology. Following the guidelines outlined by PRISMA, 160 articles were identified and categorized into six categories. The analysis highlighted a notable increase in publications within this field since 2020, coinciding with the emergence of COVID-19. Geographically, the United States emerged as the leading contributor to research in this area, accounting for 21.9% of the publications. Among the identified articles, 20.6% were classified as reviews, while the remaining 79.4% comprised research studies. Data extraction focused on publication year, last author's country affiliation, CAP source type, targeted applications, and investigated virus species. Fundamental research constituted the largest category of articles (34.4%), followed by studies exploring surface decontamination via CAP technology (18.8%). Dielectric barrier discharges (DBDs) were identified as the most prevalent CAP source employed in the studies, representing 26% of all cases. Analysis of the included experimental articles showed investigations encompassing 42 distinct viral species. RNA viruses emerged as the most extensively studied group, accounting for 76.2% of the research focus. The findings of this systematic review demonstrate the effectiveness of CAP in inactivating a broad spectrum of viruses. This includes both enveloped and non-enveloped viruses and DNA and RNA viruses affecting humans, animals, and plants. CAP-mediated viral inactivation is likely mediated by a multiplicity mechanism involving direct damage to viral particles, viral replication disruption, and host immune response modulation.

Keywords Cold atmospheric plasma · Virus · Plasma decontamination · Reactive species

Extended author information available on the last page of the article

Introduction

This systematic review was conducted in accordance with the (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) PRISMA guidelines, following a predefined protocol to ensure methodological rigor, transparency, and reproducibility PRISMA [1]. The review synthesizes current evidence on the application of cold atmospheric plasma technologies for viral inactivation, providing a structured and comprehensive overview of the available literature. Viral diseases exert a substantial influence on the global economy and society. Throughout history, viral diseases have caused widespread devastation, claiming millions of lives and profoundly impacting human civilization. Notable examples include the Spanish flu (1918–1919) [2], the Asian flu (1957–1958) [3], the H1N1 influenza pandemic (2009–2010) [4], and the ongoing HIV/AIDS crisis since the 1980 s [5]. More recent outbreaks, such as the Ebola epidemic (2014–2016) [6] and the COVID-19 pandemic (2020–2022), have further demonstrated the severe threat posed by viral pathogens to global health, economies, and societies. In addition, foodborne viruses remain a significant global concern, with over 200 diseases linked to contaminated food. Human noroviruses (HNoVs) and hepatitis A virus (HAV) are major causes of foodborne illness, often associated with contaminated fresh produce like leafy greens and berries. Such contamination frequently occurs during food handling and preparation by infected workers [7].

Viral transmission occurs through various mechanisms. During processes such as coughing, sneezing, conversation, or even exhalation, infected individuals can expel respiratory droplets harboring viruses (e.g., influenza and SARS-CoV-2). Inhalation of these droplets by susceptible individuals (respiratory transmission) constitutes one of the primary transmission modes. Furthermore, respiratory droplets containing potentially infectious microorganisms can contaminate inanimate objects or surfaces, transforming them into fomites (inanimate object surfaces that can spread infectious agents), which can serve as vehicles for transmission [8]. Conversely, other viruses, such as herpes simplex and human papillomavirus, necessitate more intimate physical contact with carriers for transmission [9]. Fecal-oral and bloodborne routes represent additional potential routes for viral propagation. Water acts as a transmission medium for many pathogens, allowing human viruses such as adenovirus, norovirus, and poliovirus to remain infectious for months. Poor water sanitation and inadequate hygiene contribute to outbreaks of acute gastroenteritis, mainly caused by viruses like norovirus, hepatitis A and E, and rotaviruses. Consuming contaminated food or water and contact with infected individuals are major transmission routes, with polluted water sources often identified as the primary cause [10]. It is important to highlight that viruses employ different transmission mechanisms, some of which may co-occur [9, 11]. To effectively reduce viral transmission, emphasis must be placed on preventing and managing viral infections. Management typically involves administering antiviral drugs targeting the viruses themselves or the host cell factors [12] or employing medications that reduce symptoms while the immune system fights the virus. However, the emergence of antiviral resistance, a consequence of viral evolution, has decreased the efficacy of antiviral treatments. As a result, preventing viral infections has become increasingly important. Mitigating antiviral resistance presents significant challenges in the therapeutic approach to viral infections. Furthermore, the diverse transmission routes of viruses expose individuals to constant danger. Consequently, implementing effective preventive measures is crucial to prevent the spread and subsequent development of viral infections. A multifaceted approach

utilizing disinfectants, chemical agents, and physical methods like filtration and ultraviolet (UV) radiation has been and continues to be a cornerstone in combating virus transmission. For instance, filtration plays a critical role in managing air quality within heating, ventilation, and air conditioning (HVAC) systems. These filters function by mechanically trapping microorganisms but not inactivating them [13]. While filtration offers a valuable tool, it does present certain limitations. The accumulation of captured microorganisms on the filter mesh can create a favorable environment for bacterial growth, necessitating frequent maintenance or replacement. Filters also increase the pressure drop within HVAC ducts, raising energy consumption. This requires the use of oversized fans to maintain airflow. Ultraviolet-C (UV-C) radiation represents another approach to virus mitigation. However, its effectiveness depends on sufficient pathogen exposure times, often incompatible with typical airflow rates within HVAC systems. Furthermore, UV-C operates on a line-of-sight principle, limiting its efficacy in complex duct networks. Finally, exposure to UV-C radiation can potentially induce skin irritation (erythema) and other adverse effects [13, 14]. The recent emergence of novel viral diseases, such as the COVID-19 pandemic caused by the SARS-CoV-2 virus, underscores the limitations of existing methods for fighting viral transmission. This has stimulated the exploration of innovative strategies, including CAP technology. CAP represents a partially ionized gaseous state generated under near-ambient temperature and atmospheric pressure conditions. CAP comprises various reactive species, including charged particles, radicals, and UV rays, capable of interacting with biological systems. Specific components within CAP, such as reactive oxygen and nitrogen species (RONS), exhibit strong antimicrobial properties [15]. These RONS act upon microorganisms through various mechanisms, ultimately leading to their inactivation. These properties of CAPs explain why a considerable number of studies focus on using CAPs for the inactivation of various pathogens, such as viruses [16–18].

Research conducted in recent years has shown promising results, demonstrating the efficacy of CAP in inactivating or reducing the viral load of a broad spectrum of viruses, including those affecting humans, animals, and plants [19–21]. However, each study in this field can be considered unique due to the use of different plasma sources (often lab-custom-made) and operating conditions (e.g. voltage, current, power), environmental conditions (such as temperature and relative humidity), inherent properties of the matrix (e.g. surfaces, liquids, bioaerosols, etc.) and the specific properties of the virus being studied. CAP treatment efficacy is demonstrably influenced by many factors, including the type of plasma source employed and the specific process parameters utilized.

CAP can be generated through plasma sources based on different architectures, such as dielectric barrier discharge (DBD), surface dielectric barrier discharge (SDBD), plasma jet, or corona discharge. DBD configurations are characterized by the presence of at least one insulating material as a dielectric barrier, which prevents the transition to a thermal plasma discharge (arc-like discharge), stopping current and spark formation [16, 22, 23]. The space between the dielectric and the electrode, or between two dielectrics, is called the gas gap [22]. When one or both electrodes are powered, and the applied voltage is higher than the gas breakdown voltage, a discharge is initiated [24]. At atmospheric pressure, DBDs are not uniform but filamentary. They are composed of a large number of high-intensity streamers (micro-discharges) that connect electrodes, often moving between and interacting with each other [16, 25]. Based on the general working principles, different arrangements can be realized. It is possible to identify two main categories: volume DBDs and surface DBDs. In the

volume DBDs, one or both electrodes are covered by a dielectric material, and the plasma discharge is ignited in the gas gap, also known as the interelectrode gap. In surface DBDs, both electrodes are in direct contact with the dielectric material, and plasma is generated on the edge of the ground electrode, which is often a mesh, in order to maximize the plasma generation surface [22, 23]. In this configuration, a part of the plasma reactive agents, such as electrons, ions, and the electromagnetic field, remains localized close to the ground electrode, limiting their direct interaction with the treated substrates. As a result, the primary agents contributing to the treatment are long-lived reactive species like ozone. The versatility of DBD configurations in terms of geometric design and operating condition settings is wide. Corona plasma sources necessitate a high-voltage (HV) electrode, such as a pin, thin wire, or a sharp edge, to generate an electric field close to the electrode that is significantly stronger than the field in the surrounding gas and ignite the discharge [16]. The corona discharges are always non-uniform. This configuration's simplicity and capacity to initiate discharge at atmospheric pressure contribute to its widespread adoption [16]. Plasma jets are a distinct category of CAP sources known for producing a stream of chemically reactive species. There are many configurations of plasma jet sources, but they all have in common that a gas discharge is operated in an unsealed electrode assembly and is projected outside the electrode assembly into the environment. The expansion of the plasma is often due to the high flow rate of a carrier or working gas (noble gases such as helium and argon) [26]. Due to their ability to produce plasmas that are non-constrained or confined by electrode limitations, these plasma sources have gained significant attention. Many different plasma jet configurations exist, and one of the possible classifications is based on the electrode arrangement. Among the main configurations of plasma jets, the DBD jet and the corona jet are notable examples [18]. A possible DBD jet architecture consists of a dielectric tube with a centered HV pin electrode and a ground metal ring electrode on the outside of the tube. A cold plasma jet is created in the surrounding air when a working gas (helium, argon) flows through the dielectric tube, and a kHz HV generator is switched on. Typically, the plasma jets only employ a power of several watts, so the power density delivered to the plasma remains low, and the gas temperature is close to room temperature [27]. Moreover, the length of the plasma plume can reach several centimeters [27, 28]. Finally, whether the substrate to be treated is far away or close to the nozzle, there is no risk of arcing due to the presence of the dielectric. These features make these plasma sources easy and practical. In a possible corona jet configuration, there is no ground electrode ring outside the dielectric tube. In this case, the tube has the only role of guiding the gas flow, and so, in this configuration, there is a risk of arcing, making them unsuitable for biomedical applications.

In addition to the plasma source design, CAPs can be generated using several gases and operated with different parameters such as voltage, frequency, and current to achieve desired outcomes [21, 29]. Voltage, frequency, and current can influence the interaction between CAP and microorganisms, such as viruses and bacteria. Indeed, all these parameters influence the power dissipated in the plasma discharge. For example, it is known that the power of plasma is proportional to the voltage applied in the discharge zone. Changing the input power means altering the composition of the plasma, and consequently, it influences the interaction between CAP and microorganisms [16, 29].

Environmental conditions are an essential factor influencing plasma physics and chemistry. In particular, the formation of reactive species is mainly influenced by relative humidity (RH). Water vapor in the air affects the production of reactive oxygen species (ROS) such

as hydroxyl radicals, hydrogen peroxide, and ozone [29, 30]. Finally, high humidity in the discharge can lead to increased electron energy losses due to inelastic collisions with water molecules, which can reduce the overall plasma reactivity or intensity [31]. Environmental temperature affects CAP, potentially altering plasma chemistry and efficiency in applications such as pollution control and sterilization by influencing electron collisions and species production [32, 33].

It is also possible to distinguish between different treatment techniques. Direct treatment is when the contaminated matrix or microorganisms are directly exposed to plasma discharge. Conversely, indirect treatment involves exposing the target (microorganisms) to the post-discharge zone with a high concentration of long-lived reactive species. An alternative strategy involves plasma-treated liquids (PTLs) as a medium for the inactivation of microorganisms.

The effect of CAP treatments also extends to specific properties of the treated matrices, such as surfaces, liquids, and bioaerosols (tiny airborne particles that originate from living things containing microorganisms), which also play a significant role.

Different properties of the substrate surface, such as surface roughness, porosity, wettability, electrical conductivity, and chemical composition, can influence the interaction between CAP and microorganisms [29]. Rough or porous substrates can realize microenvironments that shield microorganisms from direct plasma exposure [34, 35]. The presence of the liquids on the substrate can increase the concentration of some species, such as hydrogen peroxide and ozone. Moreover, the chemical composition can affect how RONS interact with the surface [36].

In the case of liquids or bioaerosols, the interaction with CAP is influenced by the liquid nature and/or the size and distribution of droplets forming the bioaerosol. When CAP interacts with liquids, many reactive species generated in the gas phase can dissolve into the liquid [37]. Some liquids, especially those containing organic matter, can neutralize RONS. Moreover, in the case of bioaerosols, the size of the particles is a significant factor in the interaction with CAP [38]. Smaller droplets have a larger surface-area-to-volume ratio, allowing RONS to interact more effectively with microorganisms in bioaerosols [39]. The distribution of the droplets should also be considered because some particles may be less exposed to RONS if the bioaerosols are unevenly distributed or clustered.

Moreover, within the context of this systematic review, it is important to consider the inherent characteristics of the target microorganisms, mainly focusing on viral characteristics. Basically, a virus is a macroscopic intracellular parasite particle that must replicate inside host cells. They hijack the host cell's machinery to generate viral replication complexes, effectively reprogramming the cell for viral progeny synthesis [9]. Viruses enter the host organism, physically contact a target cell, and then cross the cell's plasma membrane. Once inside, the viruses release their genetic material and begin the replication process while managing the manufacture of their protein via the host cell's ribosomes. Its structure consists of genetic material, DNA or RNA, surrounded by proteinaceous capsids [9] and some viruses possess an additional lipid envelope. The type of viral nucleic acid determines the way this process develops. Then, freshly created biological molecules are used in virus particle assembly, which creates infectious virions [11]. The specific characteristics of viruses largely influence the effect of CAPs and could differ from virus to virus, considering the diversity in the viral kingdom with over eleven thousand identified species [29].

This review aims to provide an overview of the field of CAP application in the context of viral interactions. The primary objective of this systematic review is to provide a map of the utilization of CAP on viruses, considering various methodological aspects, including principal plasma sources, applications, and targeted viruses.

Methods

The systematic research was conducted in adherence to the guidelines outlined by the PRISMA [1].

Documents Identification

The research for pertinent literature was conducted using two prominent electronic databases, Scopus and Web Of Science. The research on the two databases was conducted using a combination of keywords to include various terminologies related to the CAPs and the target biological agents to ensure comprehensive coverage. The exact search string applied in both databases was as follows: *("cold atmospheric plasma" OR "cold plasmas" OR "cold plasma" OR "gas plasma" OR "non thermal plasma" OR "non thermal plasmas" OR "atmospheric pressure plasma" OR "atmospheric pressure plasmas" OR "non-equilibrium plasma" OR "non-equilibrium plasmas" OR "atmospheric pressure air plasma" OR "atmospheric pressure discharge plasma" OR "atmospheric pressure air plasmas" OR "non-equilibrium plasma jet" OR "non-equilibrium plasma jets" OR "non equilibrium plasma" OR "non equilibrium plasmas" OR "non equilibrium plasma jet" OR "non equilibrium plasma jets" OR "atmospheric pressure non-equilibrium plasma" OR "atmospheric pressure non-equilibrium plasmas" OR "plasma reactor" OR "plasma torch" OR "nonthermal" OR "nonthermal plasma" OR "corona discharge" OR "dielectric barrier discharge" OR "plasma activated liquid" OR "plasma activated liquids" OR "plasma activated water" OR "plasma treated liquid" OR "plasma treated liquids" OR "plasma treated water" OR "plasma activated medium" OR "nonthermal plasma-activated solution" OR "plasma activated aerosol" OR "plasma activated aerosols" OR "plasma generated water") AND ("virus" OR "viruses" OR "bioaerosols" OR "aerosols" OR "surrogates" OR "surrogate" OR "bioaerosol" OR "aerosol" OR "*virus" OR "*surrogate" OR "*viruses" OR "*surrogates" OR "pathogens" OR "antiviral" OR "viral" OR "*phage").*

Inclusion Criteria

The systematic review covered all original studies and reviews on the interaction between CAPs and viruses published in English since 1 January 2000.

Exclusion Criteria

All publications made after December 31, 2024, were not considered. The review did not include the following: case reports, editorials, letters to the editor, short/rapid reports, highlights, symposia, abstracts, and preprints.

Selection Criteria and Data Extraction

The obtained research results were screened based on evaluating titles and abstracts. Records that appeared potentially relevant were retrieved in full-text format for a comprehensive assessment, thereby determining their definitive inclusion in this review. Reviews were taken separately. Data on the year of publication, the last author's country affiliation, the type of CAP source, and virus species were all extracted. The analysis of the identified articles revealed a distribution across six pre-defined categories:

- **Fundamentals**: basic studies on the interaction between plasma and viruses or virus constituents (e.g., proteins or RNA), or engineered viruses (e.g., such as pseudoviruses).
- **Surfaces**: use of CAPs to decontaminate surfaces from viruses.
- **Liquids**: use of CAPs to decontaminate liquids from viruses.
- **PTLs**: use plasma-treated liquids as an intermediate medium to inactivate viruses.
- **Bioaerosols**: use of plasma to inactivate virus-containing bioaerosols.
- **Reviews**: an overview of current thinking on the topic.

Results and Discussion

Number and Geographic Distribution of Articles on CAP and Viruses

A total of 5085 documents were identified. Among these publications, 109 were not in English, and 1523 were duplicated studies and were excluded. The remaining 3453 publications were scrutinized and screened based on study selection criteria. A final total of 160 publications was included: 127 original articles (79.4%) and 33 reviews (20.6%) (Fig. 1).

A comprehensive list of all identified documents is provided as supplementary Table 1. Since 2007, the number of documents has grown quickly (Fig. 2). Moreover, a rapid increase is evident from 2020; this observation is logically supported by the COVID-19 pandemic that broke out in 2019, which led to a strong global scientific effort to develop mitigation measures for the spread of SARS-CoV-2. As a result, there has been a significant increase in studies in the cold plasma community that focused on employing CAPs for viral inactivation. The global distribution of research (Fig. 3) reveals the United States as the leading contributor, accounting for 21.9% of the publications. China, South Korea, Japan, Germany and India follow at 16.9%, 13.1%, 6.9%, 5.6% and 5% respectively. All remaining countries contributed less than 5% to the literature.

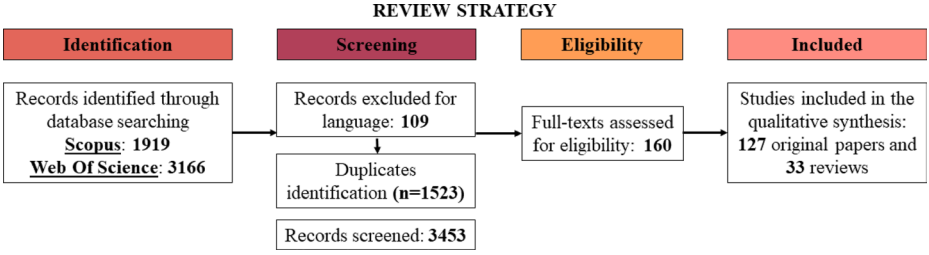

Fig. 1 Flow diagram of studies screened, assessed for eligibility, and included

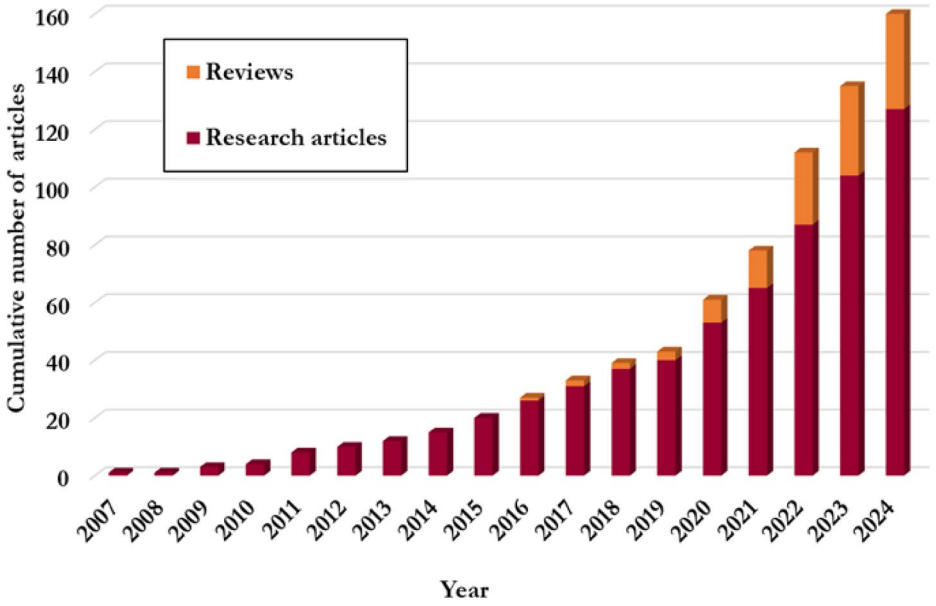

Fig. 2 Cumulative published articles on CAP technology for virus treatments

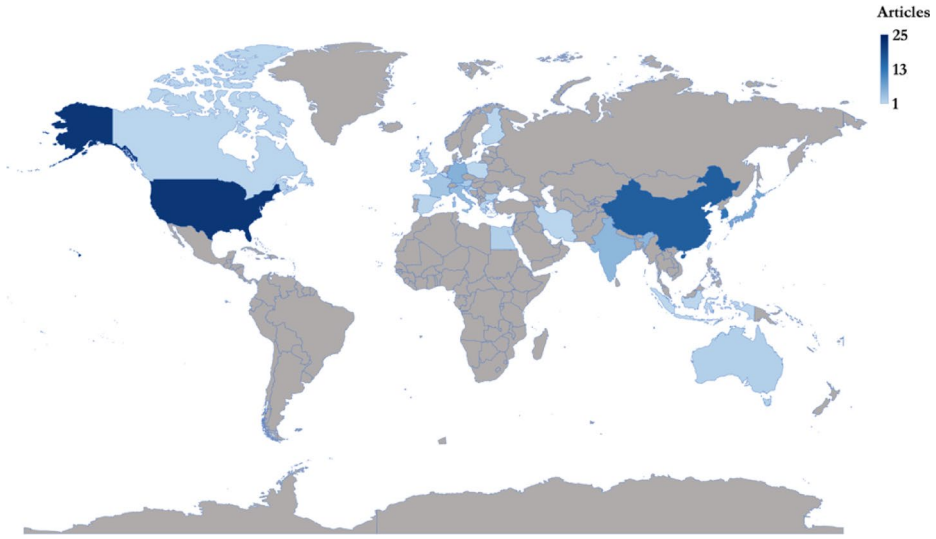

Fig. 3 Geographical distribution of identified articles

Quantitative Analysis of Articles Distributions across the Six pre-defined Categories

As illustrated in Figs. 4 and 5 and a substantial portion of the studies (34.4%) are under the category of fundamental research. These investigations aim to elucidate the fundamental mechanisms governing the interaction between CAPs and viruses or parts of the virus (e.g.,

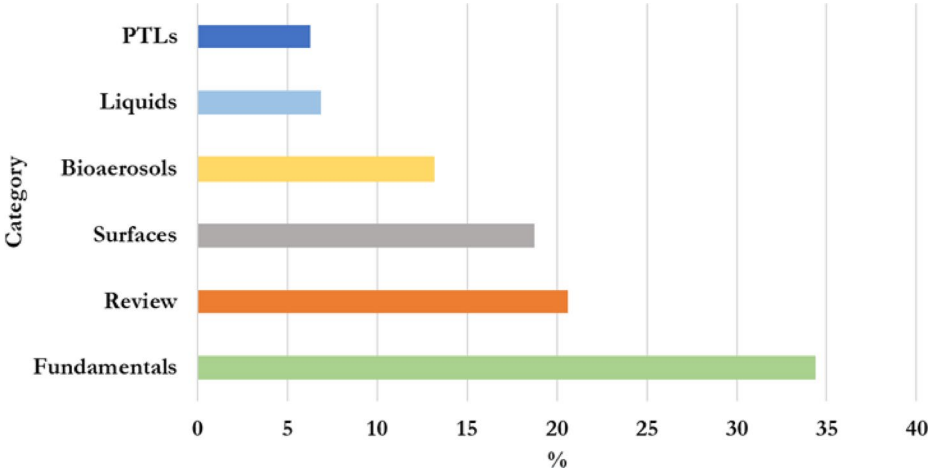

Fig. 4 Distribution of the identified articles according to the six pre-defined categories

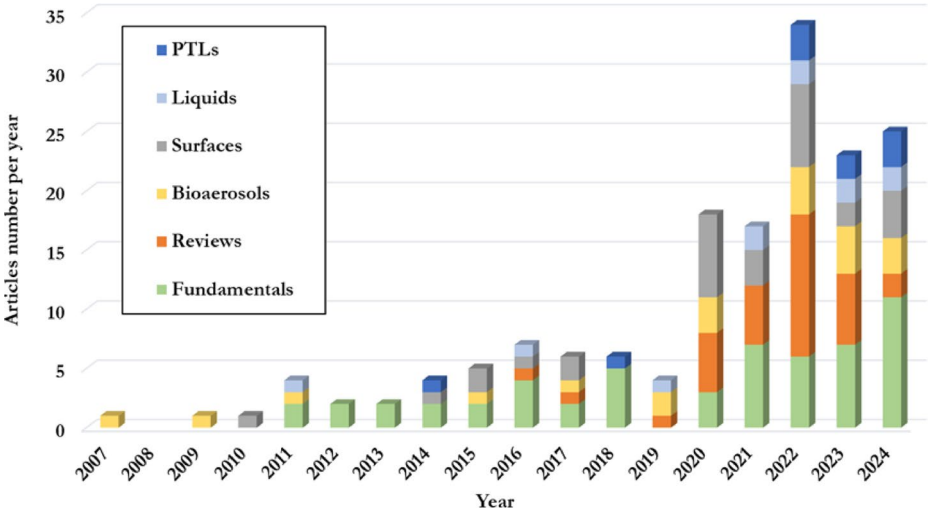

Fig. 5 Yearly distribution of the identified articles considering the six pre-defined categories

proteins or RNA), or engineered viruses (e.g., such as pseudoviruses). Excluding review articles (20.6%), the second most prevalent category focuses on the decontamination of surfaces from viruses, with 18.8% of the publications. A smaller proportion (13.1%) is dedicated to the inactivation of viruses within aerosols, an area closely associated with airborne transmission. This emphasizes the critical need for a more significant study of this very relevant topic. Studies investigating the decontamination of liquids containing viruses using CAPs and those exploring plasma-treated liquids as an intermediary approach for virus treatment are less prevalent, constituting only 6.9% and 6.3% respectively, of the total publications.

Quantitative Analysis of the Plasma Sources Identified Within the Articles

Among the CAP sources employed in the reviewed studies, DBDs emerged as the most prevalent technology, accounting for 26% of all cases (Fig. 6). DBD jets followed closely behind at 19.7%, while surface DBDs (SDBD) claimed a 15% share. The prominence of DBDs and surface DBDs can likely be attributed to their design flexibility, making them well-suited for industrial applications. Conversely, DBD jets appear to be favored in fundamental research, where their role lies primarily in elucidating the mechanisms of CAP-virus interaction. The category labeled "others" includes a diverse range of CAP sources with characteristics distinct from the categories above. These sources often represent hybrid configurations combining elements of the previously discussed technologies (e.g., the plasma source used by Sakudo et al. [40], which has two high-voltage electrodes and a ground electrode without any dielectric material). Corona sources, including corona discharges and corona jets (11% and 6.3% respectively), garnered comparatively lower usage.

Analysis of the Different Viruses Within Identified Articles

Analysis of the experimental articles revealed 42 distinct viral species investigated (a comprehensive listing of all identified viruses is included in supplementary Table 2). The IV - Single-stranded positive RNA (ssRNA+) viruses emerged as the most extensively studied category, accounting for 54.8%, as illustrated in Fig. 7-a. Moreover, 52.4% of the studied viruses belong to the non-enveloped group (Fig. 7-b). The emphasis on RNA viruses (76.2%), as highlighted in Fig. 7-c, can be attributed to their heightened public health risk due to their propensity for rapid genetic mutation. This observation can be readily under-

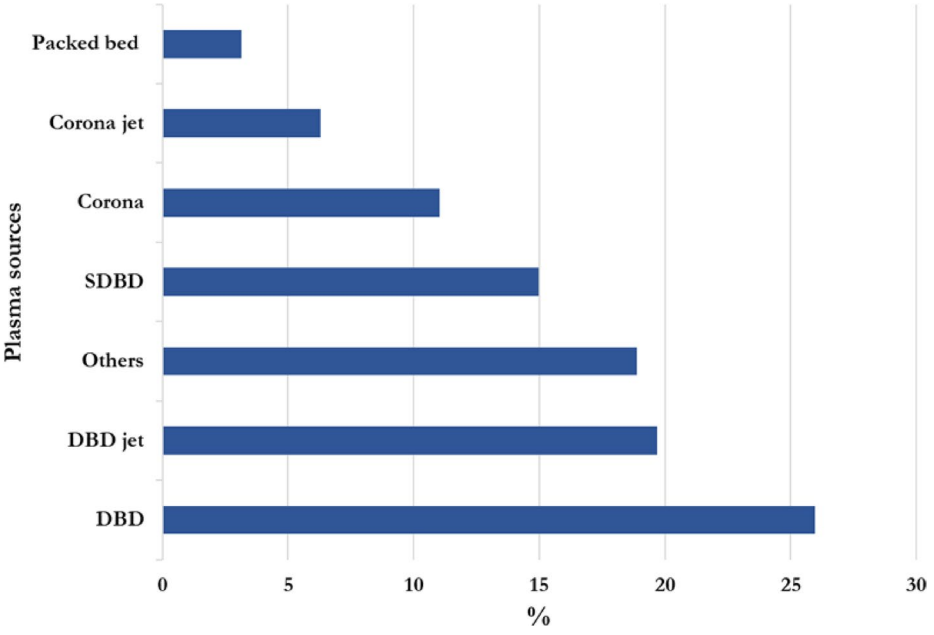

Fig. 6 Distribution of plasma sources identified within the articles. (DBD = dielectric barrier discharge; SDBD = surface dielectric barrier discharge)

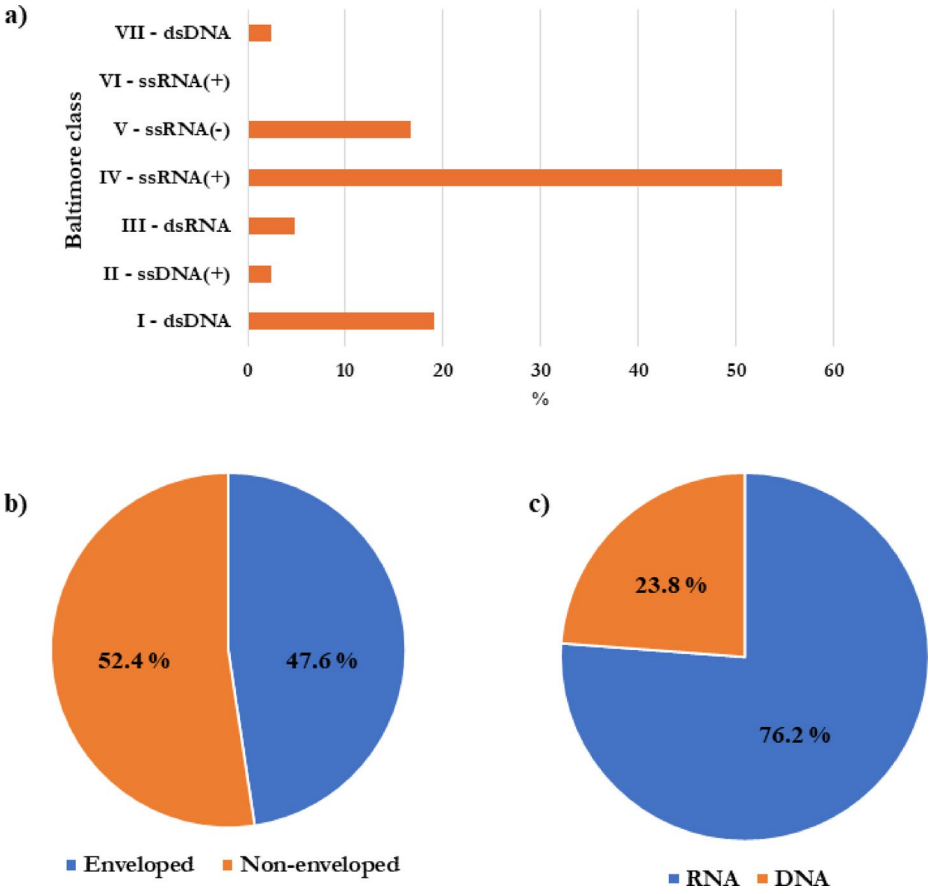

Fig. 7 – Distribution of identified viruses in the articles based on: (**a**) the Baltimore classification, (**b**) the presence of envelope and (**c**) the type of nucleic acid

stood, given the considerable focus on research on the SARS-CoV-2 virus, belonging to this particular viral class, since 2019. Consequently, SARS-CoV-2 has emerged as one of the foremost virus species under investigation in this field, together with the feline calicivirus, which is a highly contagious ssRNA + virus that primarily affects cats, and is frequently used as a surrogate for human norovirus (HuNoV), the most common cause of gastroenteritis. Moreover, other viruses that are often studied are MS2 bacteriophages, Tulane virus, and adenovirus. Finally, some studies (not included in the statistic of this section) focus on as viral proteins or RNA, or engineered viruses (such as pseudoviruses) [41–57]. The effectiveness of plasma treatments against various viruses has been extensively investigated using various techniques. Among these techniques, infectivity assays [58] such as plaque, focus-forming or end-point titration/TCID50 assays (e.g [59–70].,, and molecular methods such as PCR-based assays [71] (RT-qPCR, RT-PCR) (e.g [45, 65, 67, 72–77])., or DNA damage analysis (e.g [78]). are the most commonly used for evaluating plasma-mediated viral inactivation, while immunological assays [71] (e.g., immunofluorescence and hemagglutination tests) (e.g [40, 79–81].,) have also been used.

CAP and Viruses Interactions

The investigation of the interaction between CAP sources and viruses reveals a marked heterogeneity. Plasma sources are frequently custom-built within diverse research laboratories around the world, rendering direct comparisons challenging, but CAPs show great potential for viral inactivation.

Main CAP Constituents Interacting with Viruses

This section summarizes the main CAP components and effects discussed in reviews [7, 10, 19–21, 82–109] and fundamental papers [40–57, 80, 110–145]. Fundamental research articles and reviews demonstrate that researchers constantly work to elucidate the intricate mechanisms governing the interaction of the various components involved in plasma generation and viruses. The aim of CAP treatments in virology is mainly to inactivate viruses, and often, this process involves the disruption of viral infectivity, resulting in the virus's inability to infect host cells successfully. Intervention within the viral replication cycle is essential to achieve virus inactivation effectively. This intervention disrupts or inhibits critical stages required for successful viral infection. CAPs can interact with different viral components, including the envelope (if present), proteins (capsid proteins or surface proteins responsible for host cell attachment and entry, such as the spike protein in coronaviruses), and genetic material (DNA or RNA). Studies have demonstrated that exposure to CAPs or PTL treatments can lead to the alteration and/or destruction of these components, including viral envelope proteins, nucleic acids, and lipids (Fig. 8) [21]. Literature reveals an important role of RONS in the mechanisms underlying viral inactivation [15]. However, precisely attributing the contribution of each individual RONS species presents a significant challenge. This complexity arises from the simultaneous generation of numerous RONS, many of which possess short lifetimes, hindering their investigation. Despite these difficulties, it is well-established that RONS can exert antiviral effects by targeting viral proteins and genomes [20, 85]. Examples of these reactive species include hydroxyl radicals (.OH), superoxide radicals (O_2^{-*}), singlet oxygen ($^1O_2$), nitric oxide radicals (.NO), and excited nitrogen (N^*) [15, 85]. Their formation occurs through the interaction of free electrons with gaseous molecules. Although significant concentrations of these short-lived and highly reactive species can be obtained using CAP sources, their precise quantification and assessment are hampered by their transient nature. The contribution of long-lived RONS further enhances the inactivation of viruses [15, 45, 146]. These species are distinguished by their extended survival times before undergoing chemical interactions or transformations [16]. Examples of long-lived RONS include ozone (O_3), nitrogen dioxide (NO_2), nitrous oxide (N_2O), nitrous acid (HNO_2), and nitric acid (HNO_3) [16]. Furthermore, PTLs (plasma-treated liquids) have also been demonstrated to have various RONS, including hydrogen peroxide (H_2O_2), nitrites (NO_2^-), and peroxynitrite ($ONOO^-$) [147].

Investigating the mechanisms of CAP-mediated viral inactivation, Jin et *al* [46]. reported a significant interference of CAP treatments enriched in singlet oxygen and hydroxyl radicals on viral entry mechanisms of the SARS-CoV-2 virus. Their findings demonstrated that exposure to these RONS species resulted in alterations to the viral spike protein; indeed, the authors saw an alteration of viral spike proteins, compromising the virus's ability to bind to host cell receptors. Guo et al. investigated the efficacy of CAP and PTL treatments against

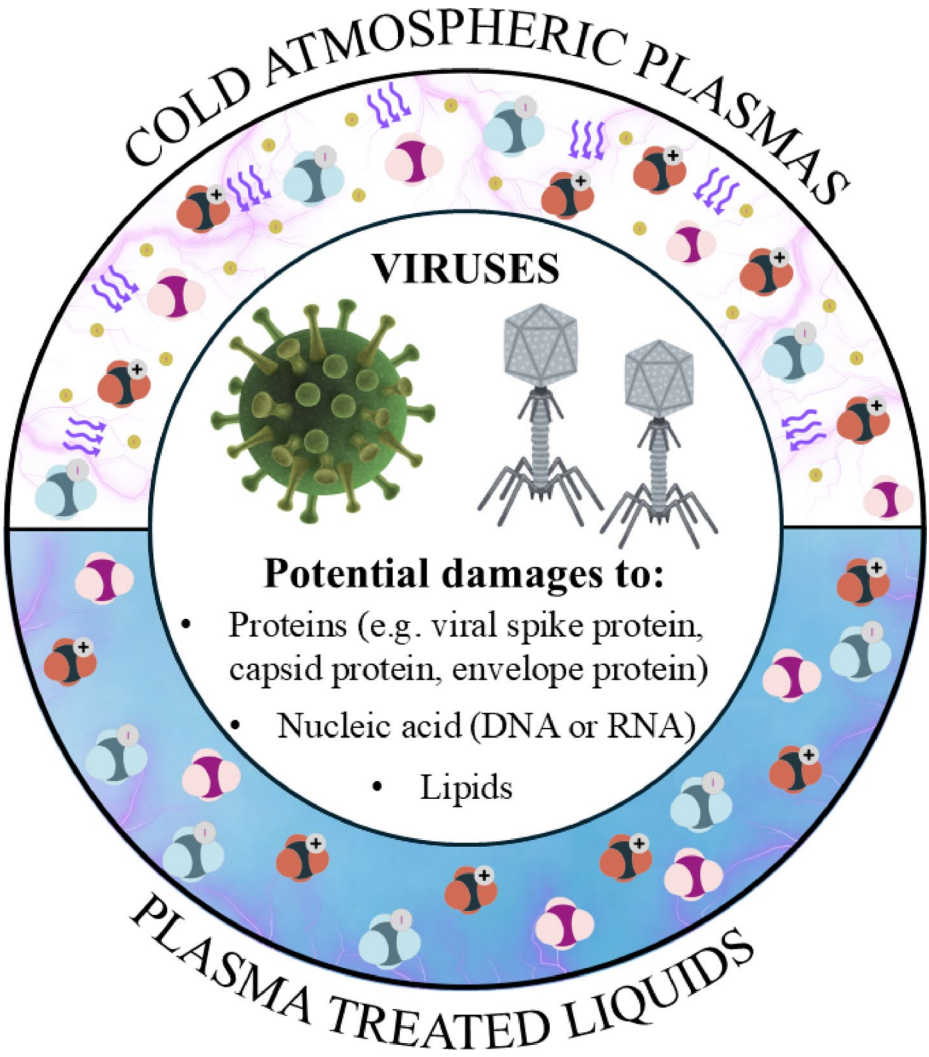

Fig. 8 Potential damages to viruses induced by CAP and PTL

various bacteriophages (T4, 174, and MS2) [130]. Bacteriophages, viruses that specifically infect bacteria, are valuable tools in scientific research. Their remarkable specificity and resilience make them ideal for use in diagnostics, where they enable rapid, sensitive, and cost-effective detection of bacterial pathogens. Bacteriophage research led to the development of the modern concept of viruses, but also laid the foundation for molecular genetics and molecular biology. By revealing the nature of viral infections and the mechanisms of heredity, phage research has influenced our understanding of life at the molecular level [148–151]. Recently, bacteriophages have been used as models for studying viral transmission dynamics in open-air environments [152]. Their analysis of DNA and protein structures revealed that the reactive species generated by CAP treatments inflicted damage on both the viral nucleic acids and proteins [130]. This observation was further confirmed by

morphological analysis, which revealed the clustering of bacteriophages following CAP treatment [130]. In a separate study by Aboubakr et al. [128], the effect of CAP on feline calicivirus (FCV) was investigated. Extended CAP exposure (2 min) disintegrated the viral capsid due to substantial oxidation of the capsid protein. Interestingly, a shorter exposure time of 15 s, while not affecting the overall capsid structure, demonstrably oxidized specific amino acids within critical regions of the capsid involved in viral attachment and host cell entry. This oxidation effectively blocked viral infection of host cells. The researchers further observed that CAP-induced oxidation could also impact viral RNA following capsid destruction. However, this effect was found to have a lesser influence on virus inactivation than capsid damage [128]. Another study investigating the mechanisms of FCV inactivation by CAP demonstrated that singlet oxygen plays a key role in inducing oxidative modifications to the viral capsid proteins [135]. Yamashiro et al. conducted a study that confirms the role of singlet oxygen in the inactivation of FCV and also underscores the contribution of peroxynitrite ($ONOO^-$) in disrupting viral RNA [132]. Similarly, Nayak et al. noted that FCV inactivation in the gas phase results from the combined effects of ozone and reactive nitrogen species (RNS), potentially including nitrogen oxides (NOx). In contrast, in the liquid phase, FCV inactivation is influenced by the pH and mainly driven by RNS, particularly acidified nitrite, while ozone has a minimal effect [153].

Shi et al. explored the interaction between CAP and the hepatitis B virus (HBV), a viral pathogen responsible for chronic liver disease transmitted through bodily fluids. Their study demonstrated that key HBV antigens were vulnerable to damage caused by RONS following CAP exposure [144]. Sakudo et al. propose hydrogen as the key agent responsible for the degradation and inactivation of influenza A and B viruses, which cause annual human infections during epidemic seasons. Their study shows that treatment with nitrogen gas plasma degrades several viral proteins, including nucleoprotein, hemagglutinin, and neuraminidase, while also damaging the viral RNA genome [40].

Additionally, Sutter et al. provided a comprehensive summary of CAP applications, highlighting its potential as a promising treatment for herpes simplex virus type 1 (HSV-1) infections. The antiviral efficacy of CAP is due to the production of RONS, which directly target and inhibit HSV-1 [87].

In addition to viral decontamination, several studies have evaluated the effects of CAPs and PTLs on infected cells. For example, CAP has been shown to reduce HIV-1 infectivity in HIV-1-infected cells by interfering with virus-cell fusion and disrupting viral assembly. It has also been suggested that CAP exposure activates cellular factors in macrophages, creating conditions that inhibit further viral entry [137]. Similarly, PTL treatment led to a reduction in SARS-CoV-2 viral titers in infected cells [154]. In addition, CAPs were found to induce immunomodulatory changes in infected cells, stimulating anti-HSV-1 adaptive immune responses, highlighting CAPs as a potential therapeutic strategy for HSV-1 infection [87].

CAP Interactions with Viruses on Surfaces

As illustrated in Fig. 4, excluding reviews and fundamental studies, one of the primary applications of CAP is for surface decontamination. The analysis of 30 studies investigating CAP-based surface decontamination reveals promising efficacy [59–63, 72–74, 78, 79, 146, 153, 155–172]. The median log reduction achieved in this application is approximately

2.7, suggesting significant potential for this decontamination method. A basic distinction between dry and wet CAP treatment can be established within this context. In dry CAP treatment, the plasma directly interacts with the dry surface; wet CAP treatment involves exposing the surface to plasma while it is partially submerged or covered by a liquid layer. The presence or absence of liquid during treatment affects the inactivation efficacy (Fig. 9). An analysis of the log reduction values reported in the 30 experimental papers of this category reveals a distinction between dry and wet CAP treatment methods. Wet treatments demonstrate a higher median log reduction (3.2) compared to dry treatments (2.85) (Fig. 9). The presence of liquid can result in additional RONS that can potentially contribute to viral inactivation, such as hydrogen peroxide, which has a well-known disinfectant power, but also nitrites that can exert an antimicrobial effect in an acidic environment. Other studies have shown that the combination of ozone (O_3) and nitrogen dioxide (NO_2) in the gas phase allows the formation of dinitrogen pentoxide (N_2O_5), which mainly leads to the formation in liquid of peroxynitritous acid, the precursor of antimicrobial agents, (.NO and.OH) [20, 63]. Peroxinitrous acid can also be formed in acid environments by the reaction between H_2O_2 and NO_2^-. According to this data, Moldgy et al. examined four different CAP sources used in air to decontaminate wet and dry surfaces (stainless steel discs) against feline calicivirus (FCV) [63]. FCV, a highly contagious single-stranded positive RNA virus, is a well-established model organism in the field of CAP-virus interactions. The study compared a direct-contact DBD source with three indirect plasma sources: a 2D DBD, a volumetric DBD, and a gliding arc discharge. These findings highlight the critical role of surface humidity in enhancing the efficacy of all four CAP-based decontamination methods [63]. However, only the direct plasma treatment approach yielded positive results for dry surface decontamination.

Furthermore, the 30 studies investigate the impact of CAPs on various surface types. A primary distinction is drawn between non-biological (N95 respirators, FFP3 face masks, plastic, aluminum, paper, polyethylene terephthalate (PET), polypropylene (PP), stainless-steel, metal, cardboard, stainless steel discs, leather football, composite leather basketball, leather baseball) and biological surfaces (raspberries, salmon, lettuce leaves, fresh oysters, raw chicken breasts, chicken breast, blueberries, romaine lettuce, fresh meats). Limited studies directly compare CAP's decontamination efficacy on biological and non-biological surfaces using the same experimental configurations and conditions. However, from the analysis of decontamination results, we observed that the use of CAPs for decontamination of biological surfaces results in a median log reduction of approximately 1.7, lower than the results obtained on non-biological surfaces (3.5). One possible explanation could be related to the presence of organic matter that may react with the reactive species produced by CAPs, reducing their effect on viruses. Moreover, the morphology of biological surfaces, particularly in the case of non-smooth surfaces, may also contribute to the reduced efficacy of CAPs [20, 173]. In general, surface porosity also plays a significant role in determining the effectiveness of treatment. Choudhury et al. investigated the performance of an SDBD source on both porous and non-porous materials contaminated with SARS-CoV-2 [168]. Their results indicated that, compared with non-porous materials such as aluminum and polycarbonate, porous substrates like KN95 masks required substantially longer treatment durations to achieve comparable viral inactivation levels (approximately 4–5 log reduction) [168].

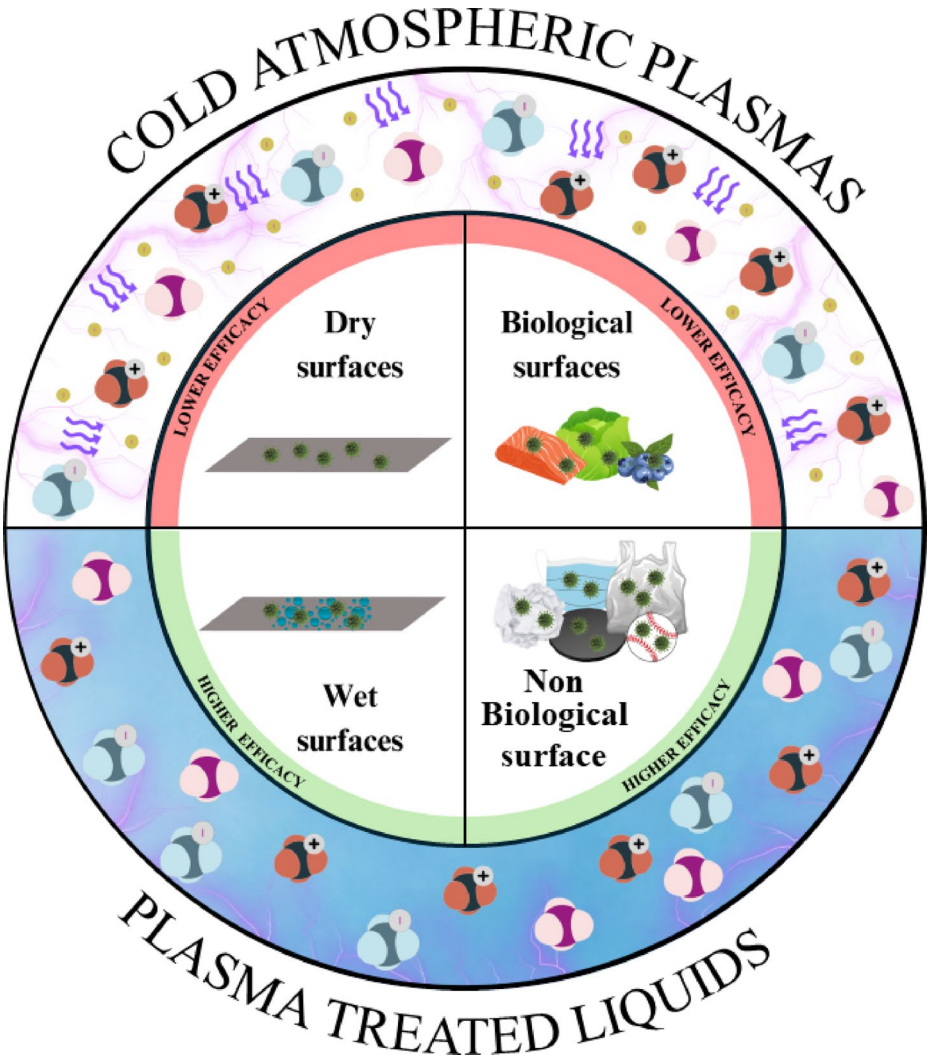

Fig. 9 CAPs and PTLs efficacy on wet/dry biological/non biological surfaces

To illustrate the application of CAPs in biological matrix decontamination, Velebit et al. [62] demonstrated the efficacy of CAP against murine norovirus (MNV) and hepatitis A virus (HAV) on aerosol-inoculated raspberries. MNV is a non-enveloped virus with a single-stranded positive RNA genome that belongs to the *Caliciviridae* family and is frequently used as a surrogate for the highly contagious HuNoV. Similarly, HAV is a non-enveloped virus with a single-stranded RNA genome that belongs to the *Picornaviridae* family. Both HuNoV and HAV have been linked to several foodborne illness outbreaks. In this case, a corona discharge plasma source was used with synthetic air, and CAP treatment resulted in a considerable 4 log reduction in infectivity in less than 5 min for MNV and around 10 min for HAV [62].

Notably, most of the documents analyzed in this application employed air as the process gas. In the rest of the studies, oxygen, argon, and nitrogen were also used as process gases [155, 156, 158, 159, 165], but air is the most interesting than other gases from a cost perspective for future applications.

CAP Interactions with bioaerosols-containing Viruses

Interest in this application has increased since 2020, despite the existence of a relevant early study published in 2007. This growing interest likely coincides with the public health crisis caused by SARS-CoV-2 and the increased awareness of airborne viral transmission. The analysis of documents [64–67, 75, 174–189] identified within this application reveals that CAP treatments applied to virus-containing bioaerosols achieve a median log reduction of approximately 2.4. DBD or its different architectures are popular for decontaminating virus-containing bioaerosols. This widespread adoption can likely be attributed to their ability to handle geometries suitable for treating large air volumes (>20 m^3/h). Investigating the efficacy of CAP technology against airborne viruses, Nayak et al. [65] employed a volumetric DBD plasma source within a wind tunnel. Their target pathogen was the single-stranded positive RNA porcine reproductive and respiratory virus (PRRV), a major swine disease. Their findings demonstrated a significant reduction in viral load, achieving a 3.5 log drop within a few milliseconds. Xia et al. [179]. used a packed-bed plasma source capable of processing an airflow rate of 170 slpm, achieving promising results with aerosolized MS2 bacteriophages (log reduction of 2.3). Notably, increasing the flow rate to 330 slpm did not influence the efficacy. A direct DBD source with an average power of less than 5 W against the SARS-CoV-2 virus was used by Bisag. et al. [67]. The authors reported the total inactivation of the SARS-CoV-2 contained in bioaerosols [67]. Moreover, a pilot study in a hospital setting showed that CAP technology, using compact DBD, effectively reduces airborne SARS-CoV-2. Rooms equipped with CAP devices had significantly lower viral presence and improved patient outcomes. The method proved safe, non-invasive, and promising as a complementary tool for infection control in healthcare environments [187].

Finally, as expected, the documents reveal a correlation between the effectiveness of CAP treatments and the contact time between viral particles and plasma or the zone rich in reactive species produced by the plasma (residence time). For the 23% of papers where residence time could be assessed, a median log reduction of 3.9 was achieved with an average residence time of less than 0.8 s, which is a compatible time to employ this technology in standard HVAC systems. The CAP's ability to achieve promising inactivation results in very short residence times (order of milliseconds) supports the hypothesis of an important contribution to virus inactivation by short-lived species such as O and OH radicals that can directly inactivate viruses or spread in micrometer droplets.

CAP Interactions with Liquids Containing Viruses and PTLs Interactions with Viruses

Although a significantly smaller fraction of research efforts focus on using CAPs to decontaminate viruses within liquid media or generate intermediary liquids for virus treatment, the observed results regarding viral inactivation are encouraging. Notably, the analysis of studies focused on the liquid application revealed a median 5 log reduction. Notably, all findings in this category pertain to the decontamination of virus-loaded water [68, 69, 76,

190–197]. This promising result is consistent with what has been shown regarding the use of CAP for decontaminating wet surfaces. A liquid environment seems to be a favorable factor for virus decontamination. Liquids in contact with plasma are rich in reactive species with strong antimicrobial power, such as OH radicals and H_2O_2, and in the presence of reactive nitrogen species in the gas phase and an acidic environment, nitric acid, nitrous acid, and peroxynitrous acid. In contrast, studies investigating the application of plasma-treated liquids (PTLs) [70, 77, 81, 154, 198–203] report a median log reduction of 3. An example of the liquid application is a corona plasma jet used by Filipić et al. for decontaminating water samples with pepper mild mottle virus (PMMoV). PMMoV is a highly resistant waterborne tobamovirus that can survive passage through the human digestive system. After 5 min, CAP totally inactivated PMMoV in water samples [193]. In previous work, the authors used the same plasma source to treat samples contaminated with potato virus Y (PVY), a common contaminant in drinking water, along with organic plant material to simulate a more polluted environment [194]. The results showed complete inactivation of PVY after a 5-minute treatment. In contrast, a shorter treatment time of just 1 min in tap water samples without organic residues was sufficient for full inactivation of PVY [194].

For the PTLs application, the idea is to produce intermediary liquids enriched with RONS for virus inactivation, as in the study proposed by Cortázar et al. [154] The authors used a DBD jet to create PTL to explore the sensitivity of the SARS-CoV-2 and PR8 H1N1 viruses (a specific strain of influenza A that has been widely used in scientific investigations for completely analyzing the influenza virus). The trials demonstrated lower viral infectivity based on in vitro analyses utilizing both isolated viruses and infected cells [154]. The authors also noted that the antiviral effect was only minimally affected by pH changes resulting from the plasma treatment of the liquid [154]. Su et al. examined the efficacy of PTLs in inactivating the Newcastle disease virus (NDV). Their study found that short-lived reactive species, such as hydroxyl radicals (·OH) and nitric oxide (·NO), along with the long-lived hydrogen peroxide, caused morphological changes in the virus, disrupted its RNA structure, and degraded its protein components [81].

Efficacy of Plasma Treatments

Figure 10 compares the efficacy of plasma treatments for viral decontamination across four categories: Surfaces, Bioaerosols, Liquids, and PTLs. Overall, higher log reductions are observed for liquids and PTLs, with values above Log R 6, indicating near-complete inactivation. Bioaerosols show more variability, with median reductions around Log R 3, while surfaces generally exhibit lower efficacy, often below Log R 3. RNA viruses tend to be more susceptible than DNA viruses across most categories. The choice of CAP source also influences performance, with corona jet and DBD configurations frequently associated with higher reductions.

The surface category, one of the most extensively studied to date, includes the largest number of plasma sources (Fig. 10), with median Log R values ranging from 2 to 6. In contrast, fewer plasma sources have been used in the other categories.

From a biological point of view, 42 virus species have been studied, with an emphasis on RNA viruses, probably their heightened propensity for genetic mutations, rendering them a significant public health concern. As illustrated in Fig. 7 and highlighted by Fig. 10, DNA viruses accounted for only 23.8% of cases, while RNA viruses made up 76.2%. The rela-

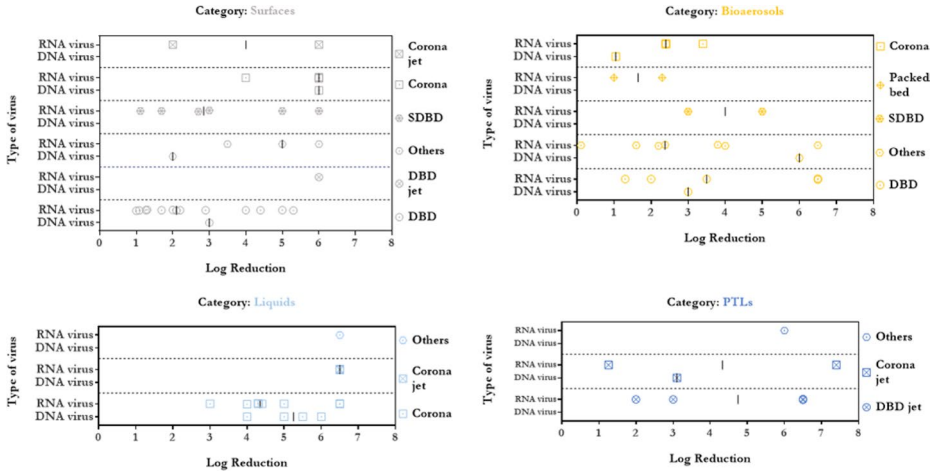

Fig. 10 Efficacy of plasma treatments in viral decontamination across various categories (Surfaces, Bioaerosols, Liquids and PTLs) based on the virus's genetic material and the type of CAP source. The black lines represent the median Log R

tively low number of articles on DNA viruses prevents drawing definitive conclusions about the greater efficacy of CAP treatments for the two respective virus categories.

Conclusions

The systematic review highlights the exponential interest in research concerning CAP-virus interaction and the potential of CAP technology for viral decontamination in various contexts.

In particular, CAPs have the potential to decontaminate inanimate surfaces through direct exposure to the plasma discharge or RONS-rich atmosphere or PTLs, potentially fighting contact-based infections. Moreover, CAPs could be a useful tool to contrast the transmission of foodborne diseases by treating food product surfaces. CAPs have also demonstrated promising results in mitigating airborne transmission of viruses, as seen during the COVID-19 pandemic. Finally, the capability of CAPs to inactivate viruses presents a promising solution for enhancing water safety, benefiting both human consumption and agricultural irrigation.

Further efforts are needed to fully understand the potential risks of using CAPs in the previously discussed contexts. For example, in the context of surface decontamination, CAPs could be an innovative strategy to fight foodborne diseases by decontaminating material in contact with food (e.g., packaging) or the food itself. In this area, careful evaluation of the potential side effects induced by food, such as chemical modifications, nutritional alterations, and organoleptic changes, is needed. In the frame of air decontamination, some devices on the market are based on the presence of DBD sources and ozone production to decontaminate microorganisms in the air. In this case, careful evaluation of ozone production is necessary because it has important antimicrobial properties, but in high concentrations indoors and over long exposure times, it can be a problem for human health. So,

efforts must ensure that ozone concentrations remain within safe limits. CAPs also showed promising potential in interactions with liquids. PTLs and liquids categories have demonstrated significant average reductions in microbial contamination. A notable application of CAPs lies in water decontamination. However, there is limited research on potential adverse effects, such as the genotoxic and cytotoxic impacts on human and plant cells. In-depth studies and risk assessments are critical to developing guidelines and protocols that optimize the advantages of CAPs while mitigating risks to human health and the environment. A thorough assessment will help determine the safety and feasibility of using CAP for water decontamination, ensuring that its benefits are maximized without compromising safety. Additionally, the stability and decay of RONS in plasma-treated liquids are strongly influenced by various factors, including plasma treatment parameters and environmental conditions. A comprehensive understanding of these factors is crucial to optimizing the effectiveness of treatments involving plasma-liquid interactions.

The application of CAP in therapeutic interventions necessitates extensive investigation and development progression before reaching clinical implementation, despite promising initial results.

Moreover, some aspects of the large-scale deployment of plasma technology for viral decontamination remain challenging. In particular, significant heterogeneity in the use of plasma devices, experimental conditions (working gas, voltage, frequency), environmental conditions, substrate type, and virus emerges from the experimental studies. Focusing only on the plasma devices and viruses used, it is evident how the reviewed studies explore a wide range of CAP sources that share underlying principles, such as DBDs, corona discharges, and plasma jets, implemented in varying structural configurations. Notably, DBDs, including DBD jets, direct DBDs, and surface DBDs, are frequently employed.

Actually, there are no standard protocols for testing the antiviral efficacy of CAP devices, which are often designed and implemented by individual research groups, making a comparison of the various proposed solutions complicated and challenging the reproducibility of the results. Some research groups have worked to optimize and standardize biological protocols to enable comparisons of the effectiveness of different plasma sources against spores of the Gram-positive bacterium *Bacillus subtilis* [204–206]. However, among the articles identified in this systematic review, those that carry out a comparative study using the same experimental conditions are rare. In addition, there is also a lack of comparative studies on viral decontamination between CAP and traditional technologies.

CAPs and PTLs can induce damage to proteins (e.g., viral spike protein, capsid protein, or envelope protein), nucleic acid (DNA or RNA), and lipids, but the exact mechanisms driving viral inactivation by CAPs are currently unknown.

Moreover, as previously discussed, the intricate interplay between various plasma components and viral particles complicates the elucidation of precise inactivation processes. The role of RONS plays in viral inactivation mechanisms is significant, yet challenging to study. Short-lived species, such as singlet oxygen and radicals, are particularly difficult to analyze due to their short reaction times (1–3 μs), and thus, a correlation between their concentrations and biological effects is not frequently reported. So, knowledge in this area is still limited and allows for extensive efforts for future research. Overall, applying CAP technology across various settings holds promise for preventing viral infections, controlling viral dissemination, and safeguarding public health.

In conclusion, the primary goal of decontamination is to significantly decrease the number of pathogenic microorganisms. Specific standards may vary depending on the context (hospital, food industry, home, etc.), the type of contaminant, and the regulations in the country. However, the World Health Organization identified different levels of decontamination: - cleaning (the physical removal of body materials, dust, or foreign material); - disinfection (the destruction or removal of microorganisms at a level that is not harmful to health and safe to handle, not necessarily including the destruction of bacterial spores); - sterilization (the complete destruction or removal of microorganisms, including bacterial spores). Considering the viral inactivation results of the different categories analyzed, it can be deduced that CAP technology is promising in disinfection.

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Declarations

Competing Interests The authors declare no competing interests.

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