Applied Microbiology and Biotechnology (2019) 103:5117–5129
https://doi.org/10.1007/s00253-019-09877-x

MINI-REVIEW

# Technical applications of plasma treatments: current state and perspectives

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Received: 28 February 2019 / Revised: 25 April 2019 / Accepted: 26 April 2019 / Published online: 15 May 2019

## Abstract

Rapidly evolving cold atmospheric pressure plasma (CAPP)–based technology has been actively used not only in bioresearch but also in biotechnology, food safety and processing, agriculture, and medicine. High variability in plasma device configurations and electrode layouts has accelerated non-thermal plasma applications in treatment of various biomaterials and surfaces of all sizes. Mode of cold plasma action is likely associated with synergistic effect of biologically active plasma components, such as UV radiation or reactive species. CAPP has been employed in inactivation of viruses, to combat resistant microorganisms (antibiotic resistant bacteria, spores, biofilms, fungi) and tumors, to degrade toxins, to modify surfaces and their properties, to increase microbial production of compounds, and to facilitate wound healing, blood coagulation, and teeth whitening. The mini-review provides a brief overview of non-thermal plasma sources and recent achievements in biological sciences. We have also included pros and cons of CAPP technologies as well as future directions in biosciences and their respective industrial fields.

**Keywords** Cold atmospheric pressure plasma · Cold plasma applications · Biological decontamination · Plasma mode of action

## Introduction

The term plasma was first used by Irving Langmuir in 1928 and describes quasi-neutral ionized or partially ionized gas in electric discharge. The plasma consists of variety of particles, neutral atoms and molecules, charged particles (electrons and ions), metastable particles (excited atoms and molecules, radicals), and photons (Bellan 2008). Depending on temperature of particles, plasma can be classified into two categories: equilibrium or thermal plasma and non-equilibrium or non-thermal plasma. The thermal plasma is characterized by an almost completely ionized gas and high temperature of at least 15,000 K (Roth 2001). The non-thermal or cold plasma is a partially ionized gas with temperature generally close to room temperature (maximum 340 K). Since the treatment by cold plasma is delivered at room temperature, damaging effects on biological tissues and thermolabile matrices can be minimized while still maintaining disinfection and sterilization efficacy. To date, several types of cold plasma have been developed. Cold atmospheric pressure plasma (CAPP) is frequently used in many life science and agricultural technologies such as medical treatment or plant and food preservations. This review presents recent developments, challenges, and future options of CAPP in biological decontamination and interactions with various tissues and organisms. In the review, CAPP chemistry, energy source generation, equipment design, and conditions are summarized together with application and modes of action in biological systems.

## Cold atmospheric pressure plasma systems

CAPP as a novel technology expanded very quickly to several industrial and medical fields (Table 1). In biological applications, the most commonly used plasmas are *Atmospheric Pressure Plasma Jets* (APPJs) and *Dielectric Barrier Discharges* (DBDs). Low-powered discharges APPJs form a wide group of small plasma torches working at low power and generating cold CAPP. APPJs consist of two concentric

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**Table 1** CAPP applications and interactions with biological systems

| Organism(s) | Plasma source | Working gas | Application | Mode of action | Reference |
|---|---|---|---|---|---|
| *Cucumber mosaic virus*, *Zucchini yellow mosaic virus*, *Watermelon mosaic virus* | C | Air | Bacteriophage inactivation | – | Štěpánová et al. (2018) |
| *Enterobacteria phage T4*, *Enterobacteria phage phiX174*, *Enterobacteria phage MS2* | S | Ar + 1% air | Bacteriophage inactivation, direct and indirect treatment, virus inactivation with PAW | Macromolecule oxidation, aggregation of bacteriophages | Guo et al. (2018a) |
| *Newcastle disease virus* | DJ with hollow electrodes | Air | Virus inactivation using PAS | Morphology changes, decrease in protein concentration, RNA degradation | Su et al. (2018) |
| *Bacillus subtilis* | C | Air | Bacterial and spore inactivation, food decontamination | – | Mošovská et al. (2018) |
| *Bacillus amyloliquefaciens* | V | Air | Bacterial and spore inactivation | Erosion of spore surface, biochemical structural damage | Huang et al. (2018) |
| *Escherichia coli* | C, S, V, W, DJ, DCJ, CD | air, He, $N_2$, $N_2$+ $H_2O$, $N_2$+ $HNO_3$, Ar | Bacterial inactivation, food and liquid decontamination, cross-stress, biofilm eradication | Cell wall damage, oxidation of antioxidants and macromolecules, collapse of antioxidant defense machinery, crumpled cells, DNA degradation/oxidation, biofilm destruction dependence on thickness of biofilm | Czapka et al. (2018);<br>Ji et al. (2018);<br>Kim and Min (2018);<br>Liao et al. (2018b);<br>Liao et al. (2018c);<br>Los et al. (2018);<br>Mošovská et al. (2018);<br>Shaw et al. (2018);<br>Sun et al. (2018);<br>Suwal et al. (2018);<br>Timmons et al. (2018);<br>Xu et al. (2018c); |
| *Helicobacter pylori* | DT | Air | Bacterial inactivation, disinfection of endoscopes | Genomic DNA damage, urease activity decline | Sakudo et al. (2018) |
| *Listeria monocytogenes* | S, DJ | Air, He | Bacterial inactivation, food decontamination, the shelf life of food | – | Kim and Min (2018);<br>Lis et al. (2018);<br>Timmons et al. (2018); |
| *Pseudomonas aeruginosa* | RT, W, DJ | He, $N_2$, air | Bacterial inactivation, synergic effect of plasma and antibiotics with no antibiotic resistance acquirement, biofilm eradication | Disruption of membrane integrity, increase of ROS levels, membrane damage by oxidative stress | Brun et al. (2018);<br>Kim et al. (2018);<br>Soler-Arango (2018) |
| *Salmonella* spp. | S, V, C, DJ, MW | Air, He | Bacterial inactivation, food decontamination, extended food shelf life | Changes in proteomic profile, overexpression of proteins related to carbohydrate and nucleotide metabolism | Kim and Min (2018);<br>Lis et al. (2018);<br>Min et al. (2018);<br>Mošovská et al. (2018);<br>Ritter et al. (2018);<br>Timmons et al. (2018);<br>Kim et al. (2019) |

**Table 1** (continued)

| Organism(s) | Plasma source | Working gas | Application | Mode of action | Reference |
|---|---|---|---|---|---|
| *Staphylococcus aureus* | S, V, W, DJ, RT, DCJ | He + 1% air, air, $N_2$, He | Bacterial inactivation, food decontamination, wastewater treatment, resistance to CAPP and antibiotics, synergic effect of NTP and antibiotics, cross-stress, combination of NTP and ultrasound, biofilm eradication | Damage to cell wall and membranes, changes in membrane potential and intracellular enzyme activity, oxidation of macromolecules, oxidative stress, ROS from NTP easier penetrate into the cells after ultrasound treatment, but preceding plasma treatment enhances oxidative response to ultrasound, biofilm destruction affected by biofilm thickness | Brun et al. (2018); Czapka et al. (2018); Ji et al. (2018); Kim et al. (2018); Liao et al. (2018a); Liao et al. (2018c); Xu et al. (2018d). |
| *Candida albicans* | KP | Ar | Biofilm eradication | Membrane disruptions and loss of intracellular content, primary inactivation of cells located at the basement of the biofilm | Handorf et al. (2018) |
| *Saccharomyces cerevisiae* | DBD glass funnel, KP | Ar | Fungal inactivation, improved metabolic activity in industrial strains, improved conversion of glucose to ethanol | protein ubiquitination, endoplasmic reticulum stress, increase of intracellular ROS, synthesis of proteins associated with stress protection, changes in membrane fluidity and conformation, increased chaperone activity, improved ROS removal, alterations in redox control | Itooka et al. (2018); Recek et al. (2018) |
| *Zygosaccharomyces rouxii* | V | Air | Juice decontamination | Cell membrane damage | Xiang et al. (2018) |
| *Aspergillus flavus*, *Alternaria alternata*, *Fusarium culmorum* | C | Air | Fungal inactivation, food decontamination | Damage of cell wall and membrane, oxidation macromolecules, damage of cell surface, increase of ROS | Šimončicová et al. (2018); Zahoranová et al. (2018) |
| *Cladosporium cucumerinum*, *Didymella bryoniae*, *Didymella licopersici* | C | Air | Fungal inactivation, food decontamination | – | Štěpánová et al. (2018) |
| *Arabidopsis thaliana* | DBD, APPJ | Air, He | Enhanced seed germination and plant growth | Increase in RONS levels and conductivity of PAW | Bafoil et al. (2018) |
| *Cucumis sativus*, *Capsicum annuum* | C | Air | Enhanced seed germination, control of seed pathogens | – | Štěpánová et al. (2018) |
| *Glycine max* | V | $O_2$, $N_2$ | Improved seed quality, control of seed-borne pathogens | Changes in seed antioxidant status and phytohormone balance, oxidation of surface lipids | Pizá et al. (2018) |
| *Lavatera thuringiaca* | DJ | He/$N_2$ | Enhanced seed germination | Changes in cuticle, decrease in contact surface angle | Pawłat et al. (2018) |

**Table 1** (continued)

| Organism(s) | Plasma source | Working gas | Application | Mode of action | Reference |
|---|---|---|---|---|---|
| *Lycopersicon esculentum* | coaxial DBD | Air | Enhanced germination rate and improved growth attributes | Higher seedling length and weight, longer and more branched roots | Măgureanu et al. (2018) |
| *Triticum* spp | V | Air | Enhanced seed germination, control of seed pathogens | Increase in water uptake, relative electroconductivity, soluble protein, and α-amylase activity | Guo et al. (2018b);<br>Los et al. (2018) |
| *Hordeum vulgare* | V | Air | Control of seed pathogens | – | Los et al. (2018) |
| *Zea mays* | C | Air | Enhanced seed germination | Increase in wettability, better water uptake | Zahoranová et al. (2018) |
| *Gallus gallus domesticus* | V | Ar | Sperm quality (count, viability, motility), growth rate, fertility | Increased acrosome and DNA integrity, upregulation of antioxidant and mitochondrial respiratory enzyme expression, increase in thyroid and growth hormones, a number of mitochondria in skeletal muscles | Zhang et al. (2018b);<br>Zhang et al. (2018c);<br>Zhang et al. (2018d) |
| *Mus musculus* | S, W, DJ, DBD | Air, $N_2$, He | Peri-implantitis treatment (embryonic fibroblast cell line MC3T3-E1), treatment of colorectal cancer, inactivation of tumor cell (LP-1 myeloma cell line) | No changes in body weight, tissue structure and organ coefficient, liver and renal function, electrolytes and glucose and lipid metabolism, increased blood neutrophils and mononuclear cells, plasma induced immunogenic cell death, changes in metabolic pathways | Kim et al.(2018);<br>Lin et al. (2018);<br>Xu et al. (2018a);<br>Xu et al. (2018c);<br>Yang et al. (2018) |
| *Rattus norvegicus domesticus* | DJ, DC glow discharge | He, Ar | Significant wound contraction, wound healing acceleration, treatment periodontitis | Accelerated wound re-epithelialization; increased angiogenesis and fibrosis, shorter inflammation phase of wound healing, reduced alveolar bone loss and promoted periodontium restoration in ligature-induced periodontitis | Chatraie et al. (2018);<br>Zhang et al. (2018e) |
| *Homo sapiens sapiens* | V | Air | Combination of plasma with AuNP to achieve synergistic anticancer cytotoxicity to human brain glioblastoma cancer cell line | Stimulation of endocytosis via ROS and membrane damage | He et al. (2018) |
|  |  | He | Inactivation of human nasopharyngeal carcinoma cell line (CNE-2Z), | Apoptosis via endoplasmic reticulum stress and | Song et al. (2018) |

**Table 1** (continued)

| Organism(s) | Plasma source | Working gas | Application | Mode of action | Reference |
|---|---|---|---|---|---|
| | | | | mitochondrial dysfunction pathway | |
| *Homo sapiens sapiens* | DJ | Air | Human osteoblast-like cell line MG63 sterilization improved bone formation—the treatment of peri-implantitis | – | Yang et al. (2018) |
| | | Ar | Reduced bacterial adhesion, tooth bleaching without adverse effect on enamel | – | Nam et al. (2018) |
| | | He, He + $O_2$ | Induction of myeloma cell apoptosis | ROS accumulation, increased CD95 expression in tumor cells | Xu et al. (2018b) |
| *Homo sapiens sapiens* | KP | Ar, Ar/$N_2$. Ar/$O_2$, Ar/$N_2$/$O_2$ | Genotoxic effect of plasma on mucosal cells | – | Bekeschus et al. (2018) |
| | | | Treatment of patients with locally advanced (pT4) squamous cell carcinoma of the oropharynx suffering from open infected ulcerations, reduction in odor and pain medication, improvement in social function and a positive emotional effect | – | Metelmann et al. (2018) |

*DBD* dielectric barrier discharges, *C* coplanar DBD, *S* surface DBD, *V* volume DBD, *W* DBD underwater, *DJ* DBD plasma jet, *DC* direct current, *DCJ* DC plasma jet, *DT* DBD plasma torch, *MW* microwave plasma jet, *RT* RF plasma torch, *KP* kINPen, *CD* corona discharge, *AuNP* gold nanoparticles, *PAW* plasma-activated water, *PAS* plasma activated solution electrodes with a flowing gas. APPJs can be categorized according to configurations and used materials as dielectric-free electrode jets, DBD jets, DBD-like jets, and single electrode jets (Lu et al. 2012). The typical geometry of APPJs is depicted in Fig. 1 a–c. Short distance between electrodes allows for low applied electric voltage, and gas flow (mainly noble gases such He or Ar) ensures low temperature character of plasma. APPJs can be supplied by direct, pulsed direct, or high frequency alternating currents (radio frequency and microwave). To increase the reactivity of plasma in some settings, small amount of reactive gas is supplemented (e.g., 1% of $O_2$). To minimize contact with the environment, the $N_2$ and air APPJs require special geometry (i.e., electrode position). APPJs can be used in direct treatment of objects, when the treated material is in direct contact with plasma or indirect treatment, when the samples do not come into direct contact with plasma but only with active particles previously generated in plasma (Weltmann and von Woedtke 2011).

DBDs are called in some cases as “silent” or “atmospheric pressure glow” discharges (Kogelschatz et al. 2003). Their defining feature is the presence of dielectric material between the electrodes. DBDs usually operate at frequencies of 50–500 kHz and voltage amplitude in the order of tens kV. The electrode gap ranges from tens of microns to several cm. *Volume* and *Surface DBDs* (VDBDs and SDBDs) are the most common DBDs configurations employed in treatment of biological systems. The VDBD configuration known incorrectly as “industrial corona” has been frequently used in industry (Pykönen et al. 2009). It consists of two parallel plates in planar or cylindrical arrangements (Fig. 1d) and operates in a uniform glow discharge mode. The SDBD contains rows of parallel electrodes (or an electrode grid) separated from the second plate electrode by a dielectric barrier layer (Fig. 1e), and plasma is formed in a non-uniform electric field. In the SDBD configuration, the discharge gap is flexible, allowing the treatment of objects of various sizes. However, the degradation of electrodes occurs, and the lifetime of the device is limited due to the contact of plasma with electrodes (Kogelschatz et al. 2003). The advantages of VDBD and SDBD are combined in *Coplanar DBD* (CDBD) (Fig. 1f) where the pairs of parallel linear electrodes with opposite polarity are covered by a dielectric barrier layer. DBDs are used in ozone generation, excimer lamps, $CO_2$ lasers, plasma displays, water purification, and air and surface modifications (Kogelschatz et al. 2003; Chirokov et al. 2005).

## Mode of plasma action

Mode of CAPP action has been studied from single cell to multicellular organisms for over 15 years (Laroussi et al. 2003; Fridman et al. 2006). The recent studies explore wide spectrum effects of CAPP, such as microbial decontamination, cancer treatment, modification of oligomeric components in plant seeds, food preservation and functionality, and microbial and animal breeding (Table 1). The interaction between CAPP and cells is very complex. It is affected by the CAPP design, the dose of energy input, working gas, and treatment time as well as biological target size and structure. The reactive oxygen and nitrogen species (RONS), charged particles, and UV radiation seem to play a key role in interactions with biological systems, although it is hard to pinpoint which component of the CAPP has the most significant impact (Brun et al. 2018; Ji et al. 2018; Šimončicová et al. 2018). It has been presumed that the physical and chemical factors could act independently or in synergy in plasma treatments. Multiple mechanisms participating in plasma-cell interactions have been described: (a) pore formation and cell erosion through etching by atomic and molecular radicals, (b) photo-desorption and subsequent chemical bond breakage, (c) direct DNA destruction triggered by UV irradiation and reactive species, and (d) formation, diffusion, and accumulation of oxygenated species that induce oxidative damage to lipids, proteins (cysteine and amino acids with aromatic rings), polysaccharides, and DNA (Takai et al. 2012; Lackmann et al. 2013; Graves 2014; Arjunan et al. 2015; Edengeiser et al. 2015; Van Der Paal et al. 2016; Brun et al. 2018; Handorf et al. 2018; Huang et al. 2018; Ji et al. 2018; Sakudo et al. 2018; Šimončicová et al. 2018).

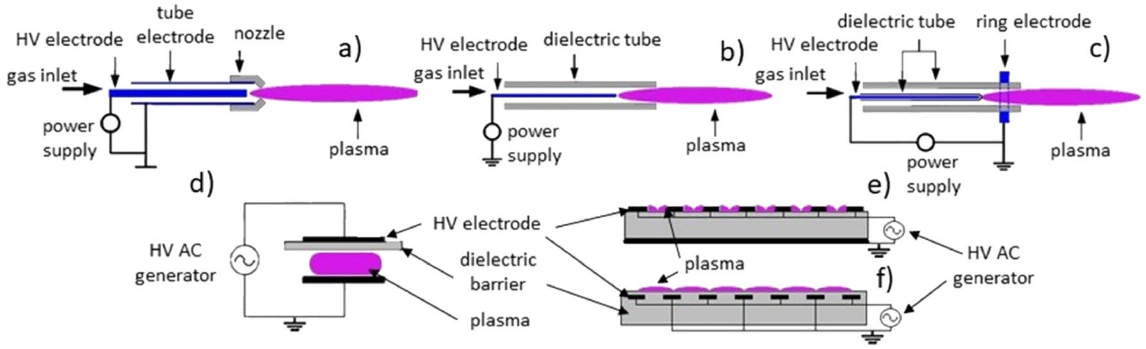


**Fig. 1** Typical configurations of APPJ: a, dielectric-free plasma jet; b, single electrode plasma jets; c, DBD-plasma jets, and DBD; d, volume–planar arrangement; e, surface and f, coplanar DBD (Kogelschatz et al. 2003; Lu et al. 2012); high-voltage alternating current (HV AC)

## Bacterial decontamination

CAPP applications in microbial decontamination has become especially important when traditional disinfection techniques fail or the inactivation of resistant bacterial strains such as methicillin-resistant *S. aureus* (Liao et al. 2018a) or spore-forming *Bacillus amyloliquefaciens* (Huang et al. 2018) has to be eradicated. The differences related to cell structure, size, cell density, metabolic activity, and ability to deal with reactive molecules in microorganisms still remain not well understood. CAPP exerts different effects on Gram-positive and Gram-negative bacteria that differ in cell envelope structures (Mai-Prochnow et al. 2016; Nishime et al. 2017). Gram-positive bacteria differ from Gram-negative by thicker cell wall and therefore, as a group display higher tolerance to cold plasma (Mai-Prochnow et al. 2016). Gram-negative bacteria possess an outer membrane that is highly sensitive to peroxidation and more prone to electrostatic disruption during cold plasma treatment (Mai-Prochnow et al. 2016). For example, rod-shaped, Gram-negative *P. aeruginosa* exhibited visible morphological deformities in cell shape while minor morphological changes were observed in Gram-positive coccal *Enterecoccus faecalis* (Nishime et al. 2017). Interestingly, *E. faecalis* exhibited overall higher sensitivity to CAPP treatment in comparison to *P. aeruginosa*, indicating possible involvement of other unspecified factors. Although, cell envelope structure plays a crucial role in microbial defense in cold plasma treatment other contributing factors need to be considered.

Bacteria are different from each other not only by cell wall composition but by shape of individual cells as well. The important elements of bacterial cell shape include the physical properties of the cell wall and the processes responsible for its synthesis and remodelling, and the balance between cell-wall extension force and turgor pressure (Campas and Mahadevan 2009; Furchtgott et al. 2011). As plasma components collide with the surface of the cell, electrostatic disruption transpires, triggering tensions in the cell wall, and mechanical rupturing and leakage of the cell content (Laroussi et al. 2003). It has been suggested that the electrostatic disruption would be intensified in rod- and spiral-shaped cells due to the enhanced field gradients on the curved areas of the cell wall (Stoffels et al. 2008). The inactivation efficacy of CAPP can be therefore influenced by the shape of bacterial cells with more resistant spherical cells (cocci) than rod-shaped cells (bacilli). Different CAPP inactivation efficacy was demonstrated in deactivation of the two Gram-positive bacteria, *L. monocytogenes* and *S. aureus*, where spherical *S. aureus* exhibited higher resistance to CAPP treatment than rod-shaped *L. monocytogenes* (Ziuzina et al. 2015).

The effect of plasma is related to numerous cell-specific factors that have not been studied or even considered in cell-cold plasma interaction. Most of studies use high concentration of bacteria grown either in liquid or in monolayers on various matrices. There are not many reports describing the effect of cell concentration and/or growth phase on the CAPP decontamination performance. In the recent study, an impact of bacteria concentration on decontamination with CAPP was reported in all tested bacteria, *S. aureus*, *S. pseudintermedius*, *Streptococcus canis*, *Pasteurella multocida*, and *P. aeruginosa* with lower concentrations being more susceptible than higher concentrations. This effect was especially profound in *S. pseudintermedius* and *Sc. canis* (Winter et al. 2018).

In comparison with planktonic cells, bacterial biofilms display increased resistance to most environmental stresses including antibiotic treatment, starvation, and oxidative stress (Bridier et al. 2015). In response to enhanced antibiotic resistance of biofilms, the research has focused on alternative approaches for an efficient inactivation and removal of bacterial biofilms. Introducing CAPP technology in biofilm eradication has proven to be a potent inactivation approach against a range of biofilm forming microorganisms (Czapka et al. 2018; Handorf et al. 2018; Soler-Arango 2018). The efficiency of CAPP inactivation was found to be bacterial species and strain dependant. The CAPP treatment reduced populations of Gram-negative *E. coli* biofilms more efficiently than those of Gram-positive *L. monocytogenes* and *S. aureus* (Ziuzina et al. 2015).

## Fungal decontamination

Significant differences were found in decontamination efficacy of bacterial and fungal cells. The experimental data confirmed that fungi were intrinsically more resistant to CAPP exposure than bacteria (Zahoranová et al. 2018). Although the eukaryotic microorganisms required longer treatment time by CAPP, they were efficiently inactivated after several minute-long exposure (Itooka et al. 2018; Recek et al. 2018; Zahoranová et al. 2018). The inactivating mechanism of filamentous fungi by CAPP resembles the one described in bacteria. Bacterial or fungal death was preceded by damage of cell envelope structures and oxidation of cell macromolecules (Šimončicová et al. 2018).

Most fungal species do not belong to human or animal pathogens but often infect plants and crops. The infection process is associated by mycotoxin production which could pose a serious threat to food safety and public health, and cause a huge economic loss (Wu 2015). Some mycotoxins are relatively thermostable, but their destruction often requires UV radiation or ozone treatment. Both ozone formation and partly also UV radiation often occur during plasma generation together with other reactive components in dependence of working gas and discharge properties. The CAPP has become a hot candidate in non-thermal and non-chemical mycotoxin detoxification strategy (Hassan and Zhou 2018). It has been successfully used to degrade deoxynivalenol, zearalenone, enniatins, fumonisin B1, T2 toxin, and sterigmatocystin (ten Bosch et al. 2017). Almost complete degradation of cancerous aflatoxin by CAPP has been achieved in corn (Shi et al. 2017) and nuts (Siciliano et al. 2016).

## Plasma agriculture and food safety and functionality

CAPP has demonstrated efficacy in decontaminating food like meat, poultry, fruits, and vegetables. Non-thermal plasma proved to be a suitable method for decontamination of food surfaces as well as liquid food without compromising the safety and quality attributes (Table 1). Plasma can also be generated in liquids, but special configurations are required for plasma discharge in water such as pulsed corona, arc, and spark (Misra et al. 2016). Plasma can be employed in water (Ji et al. 2018) or juice decontamination (Xiang et al. 2018), and in preparation of plasma-activated water (PAW) that contains active species used to treat biological material (Guo et al. 2018a; Suwal et al. 2018; Xu et al. 2018b). Many studies have shown the effective use of CAPP for decontamination of liquid food such as milk (Coutinho et al. 2018), apple juice (Xiang et al. 2018; Liao et al. 2018b), and orange juice (Groot et al. 2018).

Food safety requires not only microbial inactivation, mycotoxin, and pesticide removal but also long-term preservation. Cold plasma can degrade pesticide residues on fruits or vegetables (Phan et al. 2018). Some of the benefits of CAPP in food industry could be attributed to CAPP-mediated changes in food chemical components and functionality, such as flour rheological properties (Bahrami et al. 2016). The effect of CAPP on food qualities, e.g., pH, proteins/enzymes, carbohydrates, lipids, polyphenols, vitamins, and antioxidant capacity, have been recently reviewed by Coutinho et al. (2018), Cullen et al. (2018), Muhammad et al. (2018), and Pankaj (2018).

Several recent studies have demonstrated that CAPP treatment improved germination rate of many types of seeds (Table 1), and this could eventually enhance food and feed production. Plasma treatment of seeds causes changes in their surface properties, resulting in better seed wettability and water uptake, and consequently increased germination (Zahoranová et al. 2018). Contrary to microbial inactivation by RONS, these reactive species could increase seed germination in plants, and trigger significant changes in amylase, peroxidase, and superoxide dismutase activities (Zhang et al. 2018a). The indirect interaction of reactive species in PAW during irrigation has been demonstrated to enhance growth of radish, tomato, and sweet pepper plants in controlled conditions (Sivachandiran and Khacef 2017).

## Plasma medicine

In plasma medicine, treatment of small areas has led development of special microplasma geometries (Foest et al. 2006). The non-thermal plasma has been employed in microbial and viral inactivation, treatment of various skin diseases, wound healing, blood coagulation, teeth whitening, and antitumor therapy without significant impact on normal cells (Bekeschus et al. 2018; Nam et al. 2018; Saadati et al. 2018; Xu et al. 2018c). Cancer cells differ from normal cells in metabolism and signalling during oxidative stress. They have higher baseline ROS levels and higher expression of scavenging enzymes. The additional increase of RNOS by plasma exposure is therefore more detrimental to them than to normal cells that are able to defend themselves against exogenous ROS and maintain ROS levels below threshold associated with cell death (Graves 2014).

## Animal and microbial breeding

Plasma is considered a powerful mutagenesis tool. The plasma induces faster and greater DNA damage *in vivo* than conventional mutagenesis tools (Zhang et al. 2015). To date, several reports have published the isolation of mutants after non-thermal plasma exposure. CAPP was successfully employed in generation of *B. subtilis* mutants with a 35% increased yield of recombinant alkaline α-amylase (Ma et al. 2015), *Schizochytrium* strain with 1.8-fold increase of docosahexaenoic acid (Zhao et al. 2018), and *Streptomyces bingchenggensis* strain with 2-fold increase of 5-oxomilbemycins A3/A4 (Wang et al. 2014). *S. cerevisiae* mutants isolated after APPJ treatment displayed changes in cell membrane structure, increase in hexokinase 2 activity, and conversion of glucose to ethanol (Recek et al. 2018).

Non-thermal plasma has been recently employed in animal breeding experiments in which reproductive and embryonic cells as well as young animals have been treated by plasma. DBD plasma treatment of chicken sperm has improved viability, motility, acrosome and DNA integrity, and ultimately the total fertility (Zhang et al. 2018b). Chicken eggs were also subjected to plasma treatment. Four-day-incubated fertilized eggs treated with plasma exhibited higher growth rate in chickens after hatching, and significant increase in growth and thyroid hormones (Zhang et al. 2018c). The plasma treatment of fertilized eggs improved male reproductive capacity by improvement of sperm count and motility, but no effect on female reproduction, such as egg-laying rate and egg weight, has been observed (Zhang et al. 2018d). While plasma treatment has promoted chicken embryonic development, the prolonged plasma exposure resulted in dose-dependent embryonic death (Zhang et al. 2017).

## Perspectives and limitation

Plasma treatment provides many advantages, but also limitations (Fig. 2). Non-thermal plasma that operated at low pressure required relatively high investment costs. These initial expenses, maintenance, and servicing costs had been significantly reduced in CAPP generated in ambient air. CAPP is often described as a versatile, rapid, cost-effective, environmentally friendly, energy and water saving technology. It represents a chemical-free process that is more flexible and efficient in decontamination in comparison to pharmaceuticals. The CAPP treatment of antibiotic resistant bacteria could therefore constitute a promising alternative to tackle multidrug resistance.

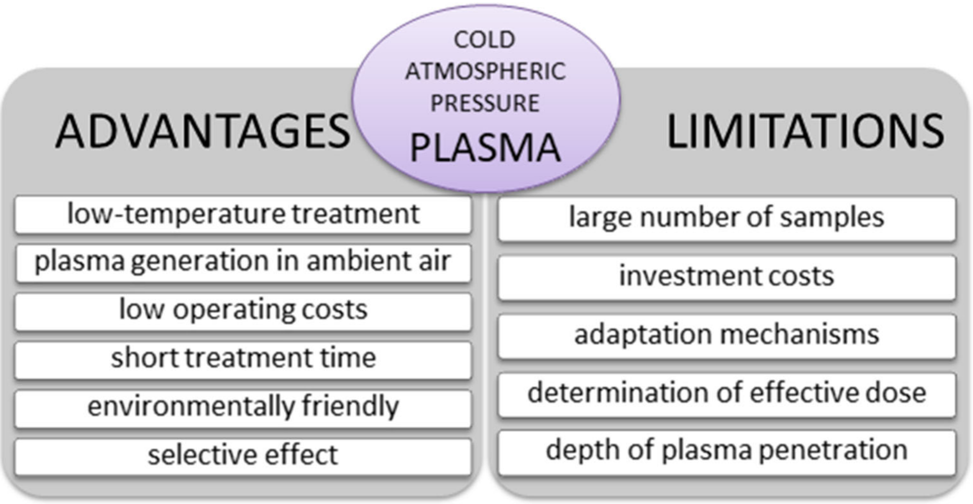
Although, non-thermal plasma is currently employed in various medical treatments, industrial CAPP application in decontamination still remains problematic. One of the major problems is plasma dose determination that could be applied in treatment protocols. An effective dose of plasma is defined by plasma source configuration, working gas composition, biological target structure, and dose determination with maximal positive effect without matrix damage. Matrix surface structure itself also influences plasma treatment effectivity. This could be especially pronounced during decontamination treatment of uneven surfaces where plasma treatment may not be as effective. The rough surfaces often hide bacterial cells that could escape plasma exposure. Moreover, bacteria can form aggregates, colonies, or biofilms that protect bacterial cells hidden inside. This contributes to incomplete decontamination since plasma particles exhibit limited ability to penetrate deeper layers of biological material and tend to remain closer to surface.

There is not a unique prototype device for all the applications, but a variety of designs and operating conditions makes it harder to pinpoint all the advantages and disadvantages. For example, APPJ can be the advantageous tool in some fields like medicine and dentistry, where it can be employed in localized decontamination treatment, plasma-induced blood coagulation, wound healing, cancer treatment, and increase of implant biocompatibility. However, in other fields such as food industry, treatment of large and heterogenous surfaces as well as high productivity has to be taken into consideration. The requirement of flowing working gas and small volume of plasma are the limiting factors for design and application of APPJs. DBDs, on the other hand, are more beneficial in treatment of large surfaces and high numbers of samples of different sizes and shapes. The advantage is a minimum or no working gas, high power density of generated plasma, and short exposure times. Most of the plasma devices have been designed for small scale treatments. To successfully transfer plasma technology into industrial settings would require development of such plasma source configurations that enable treatment of a large amount of material in continuous production. The scaling up to industrial (continual) levels could be achieved by attachment of multiple discharge units.

## Conclusion

CAPP technologies in biological sciences have undergone a very dynamic progress in last decade, especially in medicine, food industry, and agriculture. Many benefits of plasma treatment have been frequently accompanied by limitations, such as scaling-up for continuous production, which have to be addressed in future development of novel CAPP technologies. High variability in plasma configurations can be considered both beneficial and limiting. Benefits are related to high number of different plasma sources. However, this can complicate research of plasma-biological target interactions. The plasma

**Fig. 2** Advantages and limitations of plasma treatment



interaction with biological objects can also have adverse effects that have to be considered.

**Funding information** This work was supported by the Slovak Research and Development Agency under the contract no. APVV-16-0216.

## Compliance with ethical standards

**Conflict of interest** The authors declare they have no conflict of interest.

**Ethical statement** This article does not contain any studies with human participants or experimental animals performed by any of the authors.

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