Potential Agricultural and Biomedical Applications of Cold Atmospheric Plasma-Activated Liquids With Self-Organized Patterns Formed at the Interface

Zhitong Chen, *Member, IEEE*, Rong-Guang Xu, Peijian Chen, and Qiu Wang

***Abstract*— Cold atmospheric plasma (CAP) has become a topical research area due to its diverse applications in agriculture, medicine, environment, materials, energy, nanotechnology, and other fields. Plasmas in contact with liquids form marked sensitivity patterns at the interface depending on controlling parameters, including gas species, driving current, gas flow rate, gap length, and electrolyte conductivity. This review overviews basic aspects of plasmas inducing self-organization including computational and experimental studies and potential applications of such plasmas-treated liquids in agriculture and medicine. Representative experimental evidence of self-organized pattern (SOP) in diverse types of plasma discharges is reviewed. Generation and transport of reactive species in SOP plasma and SOP plasma interacting with liquids are introduced and discussed from their potential applications in agriculture and medicine.**

***Index Terms*— Cold atmospheric plasma (CAP), food safety, plasma agriculture, plasma medicine, plasma-treated liquids, self-organized pattern (SOP).**

I. Introduction

In GENERAL, self-organization is related to the spontaneous transition process from a stable state to a pattern in a spatially extended system [1]. It is fascinating and complex phenomena generally observed in both technological and natural contexts, within multiple varieties of physics, chemistry, and biology [2], [3]. Representative examples of self-organization phenomena are those studied in magnetohydrodynamics (MHD) stability and fluid dynamics, such as Rayleigh–Bénard convection and Taylor–Couette flow [4], which are responding to reaction–diffusion systems. Patterns are produced by activator inhibitor modes [5], [6], which share important similarities with plasma system-generating patterns [7]. The patterns formed at the interfaces are luminous plasma filaments displaying particle-like behavior, such as generation, dynamics, annihilation, scattering, and collective effects resulting into self-organized structures. The plasmas are formed and sustained by electron multiplication in the volume, combined with secondary electron emission by the dielectric surfaces. SOPs appear due to filamentary discharges first forming where memory charges have been previously deposited, while discharges cannot form in the vicinity of these filaments. This mechanism of activation–inhibition results into filament patterns which are typical of reaction–diffusion systems. Various types of self-organization phenomena have been addressed in a number of plasmas, such as dielectric barrier discharge (DBD), gas flow stabilized discharges, high-frequency discharge, discharges with liquid electrodes, and resistively stabilized discharged [8]–[12]. According to Müller, patterns of spots occur if a layer (electrode) contacts with a resistive medium, and it is associated with S-shaped voltage–current characteristics [13]. Many articles on numerical models have indicated that the crucial feature of the analysis is bifurcation theory [14]–[16]. Although numerical models for the self-organized pattern (SOP) formation in discharge plasma have been proposed, the experimental conditions for SOP formation have not been completely clarified. Bruggeman *et al.* [17] employed the electrical and optical diagnostics to investigate atmospheric glow discharges with the liquid anode. Wilson *et al.* [19] noticed a self-rotating atmospheric discharge with low current between a water anode and a metallic cathode generating a ring-like anode spot, which was one similarly observed by Miao *et al*. [18]. Li *et al.* [20] studied spotted anode layers in a glow discharge at atmospheric pressure with miniature argon flow and a water electrode. Upon varying gap width and discharge current, several SOPs were observed on the anode layer in glow discharge at atmospheric pressure, such as single-ring, diffuse-disk, wheel-spokes, disk-ring, and radial-stripes patterns. Gaisin [21] studied the electrical characteristics of large current discharges with a liquid anode. The effects on electrolyte composition/concentration, interelectrode spacing, current, and the diameter of the metal cathode were elucidated,

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Zhitong Chen and Rong-Guang Xu are with the Department of Mechanical and Aerospace Engineering, The George Washington University, Washington, DC 20052 USA.

Peijian Chen is with the State Key Laboratory for Geomechanics and Deep Underground Engineering, School of Mechanics and Civil Engineering, China University of Mining and Technology, Xuzhou 221116, China.

Qiu Wang is with the State Key Laboratory of High Temperature Gas Dynamics, Institute of Mechanics, Chinese Academy of Sciences, Beijing 100190, China (e-mail: wangqiu@imech.ac.cn).

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and different discharge SOPs were observed. Laroussi and Lu elucidated ac-driven discharges between a water electrode and a metal disk, and noticed distinctive patterns that depend on the electrodes' polarity [22]. During the plasma process, SOP is important to extend applications of plasma–liquid interactions [23]–[25]. Recently, lots of plasma discharges at the liquid surface/interface have been investigated related to applications including nanoparticle and materials synthesis, agriculture, foods, medicine, and others [26]–[31].

In addition, the treatment of liquid media with plasma generates plasma-treated liquids that maintain the major biological effect of plasma containing ROS and RNS [32], [33]. The complexity of reactive species in plasma-treated solutions with their reactivity and stability not only gives a challenge but also establishes plasma-treated liquids as a synergistic and unique sterilized and therapeutic approach [34], [35]. The main aim of this review is to summarize fundamental aspects of SOP plasma and to describe their potential applications in agriculture, food safety, and biomedicine. To this end, theoretical, computational, and experimental studies of SOPs in plasma discharges are presented and analyzed. This review is organized as follows. Section II elucidates the general concepts and experimental investigations of plasma self-organization. Section III considers the theoretical modeling of self-organization in plasma discharges. Some theoretical methods employed for the study of SOP formation are presented, and followed by established plasma discharge models. Section IV addresses the mechanisms of SOP plasma-treated liquids. Section V explains the potential agricultural applications of SOP plasma-treated liquids. Section VI the overviews biomedical potential applications of SOP plasma-treated liquids. This review ends with a conclusion and an outlook.

II. Self-Organization in Plasma Discharges

Plasma self-organization is more often observed at interphases, such as those over the solid and liquid electrodes [36]. SOPs in plasma discharges on liquid surfaces are more recognizable, especially when conductive liquid acts as an anode or a cathode. Moreover, plasma above the liquid is characterized by two distinctive phenomena: local (across the interface) and global (along with the interface). A representative depiction of plasma discharges between liquid and a metal pin is presented in Fig. 1(a). It is obvious that the typical plasma structure is a glow discharge with an anode glow (AG) region, a positive column (PC), a Faraday dark space (FDS), a negative glow (NG), and a cathode fall (CF). Many features are similar to atmospheric glow discharge between liquid/solid electrodes, suggesting that this discharge is the normal glow with an atmospheric version [36]. Plasma–liquids interphase is subject to perturbations. The phase change of the electrode material is generally neglected in the solid electrode research, while these phenomena might play a major role in discharges with liquid electrodes. In addition, while reactive species seldom interact below and across the surface in plasma-materials processing, which might be solvated and react in the liquid [4]. Representative different anode patterns are shown in Fig. 1(b). The obtained self-organization patterns include square/hexagonal

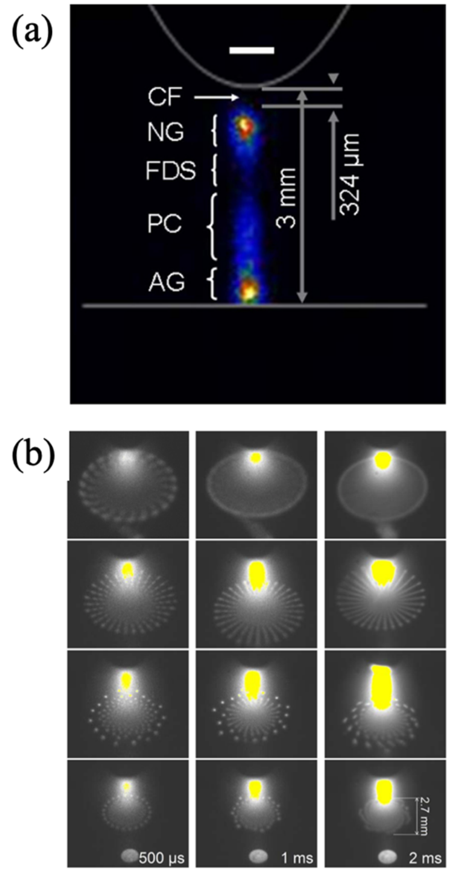

Fig. 1. (a) Single-shot photograph of the discharge structure with the liquid anode (reproduced from [17]). (b) Anode patterns generated at different conductivities and exposure times (reproduced from [39]).

superlattices, square-lattices, square-textures, hollow hexagonal, rotating-wheels, and multiarmed spirals [37], [38]. The formation of these patterns depends on the number of spots that can form stripe patterns.

Fig. 2 presents the effect of discharge current, voltage, and air gap on SOP plasma. In Fig. 2(a), a schematic representation of the glow discharge setup is capable of producing well-defined SOPs at the liquid interface. Anode (thin copper plate, thickness: 0.2 mm, and diameter: 22 mm) was placed at the bottom. About 6-mL DI (deionized) water was added to the well. The tungsten cathode (diameter: 2 mm) was then set above the DI water surface. A ballast resistor (90 kΩ) was connected between the cathode and the DC power supply unit. Voltage is applied between cathode and liquid anode, and a small (1–2 mm) gap between the cathode and liquid surface accommodated a bunch of SOPs plasma. In Fig. 2(a), the current–voltage characteristics affecting SOPs are divided into four stages. Stage I: a single filament following the initial corona discharge; Stage II: drastically enhanced heat radiation; Stage III (transition stage): an unstable state; and Stage IV: the multifilament pattern. At stage IV, the discharge plasma stretches out to a large number of discharge filaments and stabilizes at the multifilament stage at liquid media surface (SOPs). Complex shapes consisting of confocal and radial lines with different densities can be generated, and elements of axial/radial symmetry can be seen. Current and electrolyte

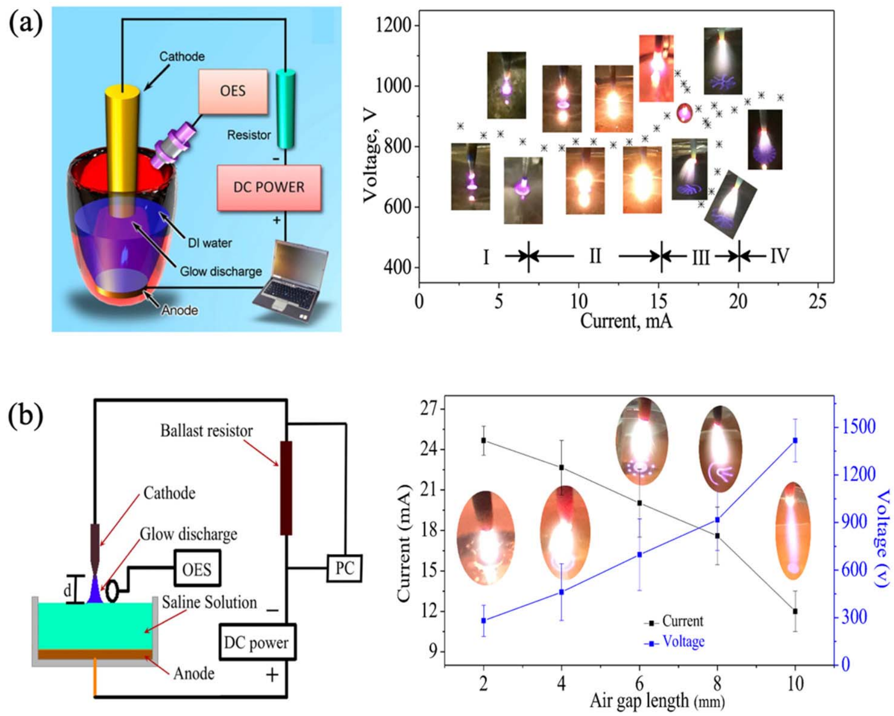

Fig. 2. Effect of experimental setups and conditions on SOPs I. (a) Experimental setup (left) and the current–voltage characteristics affecting SOPs are divided into four stages (right) (reproduced from [24]). (b) Experimental setup (left) and air-gap lengths affect SOPs using SS anode (right) (reproduced from [25]).

conductivity play important roles in generating SOPs in glow discharge [40]. Miao *et al.* [18] and Wilson *et al.* [19] have indicated that there was a small circular shape on the anode spot when the discharge current was 10 mA. When the current increase from 15 to 25 mA, the anode spot became a ring-like structure. The near anode plasma self-organization will be observed with further increasing the discharge current.

Fig. 2(b) shows the effect of gap lengths on atmospheric glow discharge on liquids electrodes. Different air gap lengths (2–10 mm) between SS anode and a metal pin cathode were considered for studying SOP at the liquid surface. The stable SOP can be observed at the liquid interface at a 6-mm air-gap length. The discharge pattern with low voltage and high current represents a single filament at a 2-mm gap. The anode spot turns into a double ring-like structure at a 4-mm air gap length. Different types of SOPs appear above the liquid media surface at 8-mm air gap length. Similarly, Verreycken *et al.* [39] reported SOPs observed with the electrode separation of 5 mm. Given these results, the SOPs of the liquid anode depend on the gap length.

SOPs at different conductivity and exposure time are shown in Fig. 3(a). Individual small spots compose the stripe patterns at larger exposure time. Radial stripes become a more homogeneous middle part with encircling stripes, when the liquid electrode's conductivity increases. These authors also show a descending trend in voltage with an increasing conductivity. Due to voltage decreasing with increasing conductivity, plasma temperature drops with decreasing current [17]. In addition, liquid types also affect SOPs due to their different conductivity and the negative ions resulting from electron affinity [41]. Fig. 3(b) shows the effect of gas type on SOPs formation. The anode SOPs are observed in air sheath flow, not in N_2 sheath flow. Different patterns are observed in O_2 sheath flow, and the patterns randomly change. Thus, O_2 sheath flow highly affects the anode pattern structure. On the other hand, the ring-like structure in air and N_2 mixture (not in pure N_2 or He) was observed by Wilson *et al.* [19]. Given the above results, the appearance of the SOP on the anode surface might depend on the gases. The authors also mentioned that the pattern formation depended on the electrolyte's temperature, namely, the amount of electrolyte vapor (consisting of electronegative gases) in the gas in the gap [42], [43]. Electronegative gases usually capture free electrons and generate negative ions in a discharge, which might cause changing the number of electrons near the liquid electrode surface. In a liquid electrode (such as water or SS) discharge process, the gas [such as hydrogen (H_2), chlorine (Cl_2) or oxygen (O_2)] will appear at the liquid surface owning to the electrolysis [44], [45]. Although the mechanism of pattern formation affected the gas is not yet completely understood, the O_2 existence definitely influences the anode pattern. The effect of pH on SOPs is shown in Fig. 3(c). Plasma induces changes on an electrolyte anode by the change in pH. The results indicate decreasing pH with the types of patterns formed: rings, double-rings, or spots. Thus, the continuous operation of the plasma, decreasing the liquid pH values, and increasing electrolyte conductivity, results in increasingly constricted anode SOPs.

III. Theoretical Modeling of Self-Organization in Plasma Discharges

From a theoretical point of view, nonlinear chemical dynamics combined with kinetically appropriate feedback loops

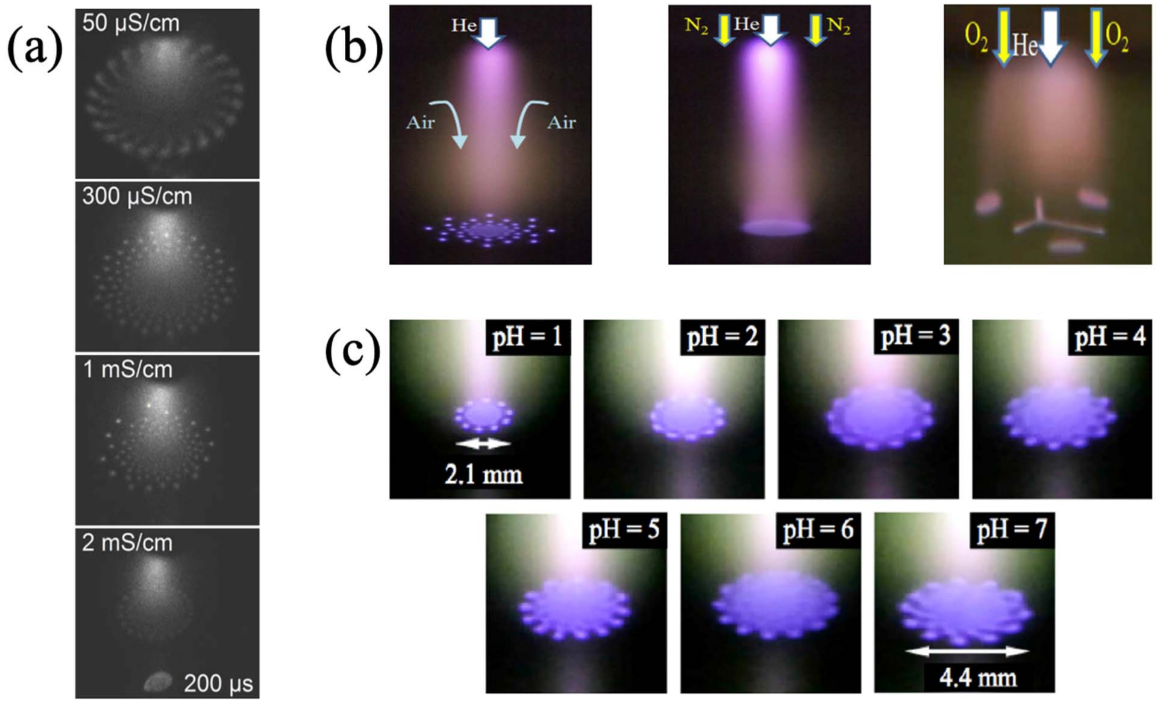

Fig. 3. Effect of experimental conditions on SOPs II. (a) Anode patterns with different conductivities at 70-mA and 200-μs exposure time (reproduced from [39]). (b) Effect of the gas species around the discharge on SOP: air (helium flows through ambient air, and exposure time for the photographs is 1/30 s), N_2 (sheath flow of 1000 sccm, and exposure time for the photographs is 1/30 s), and O_2 (sheath flow of 1000 sccm, and exposure time for the photographs is 1/500 s) (reproduced from [46]). (c) Variation patterns as a function of electrolyte pH (at a 6-mm interelectrode gap and 7-kHz frequency) (reproduced from [47]).

(transport phenomena, for instance) in an irreversible process can lead to SOPs. The SOP in plasma is also an example among such universally observed phenomenon. Physically, plasma is described as a compressible, reactive, and electromagnetic fluid [3], [48]. In plasma discharge processes, plasma is assumed to be in equilibrium chemically but in nonequilibrium thermodynamically in the presence of large field gradients. Essentially, the plasma discharge processes are inherently a multiscale phenomenon with multiphysics involved which make numerical simulation a severe challenging task. With the atomistic details and quantum mechanical effects being neglected, the plasma is conventionally modeled at the continuum level with a set of assumptions to simplify the real-world problems. Of particular relevance for the modeling are drift-diffusion models and nonequilibrium plasma flow models [4]. In the following, we will be mainly concerned with computational studies of SOPs in: 1) plasma flow model and 2) multiple solutions in cathodes of glow and arc discharges.

In addition to the fluid description in chemical equilibrium and thermodynamic nonequilibrium, the plasma model is based on the following assumptions [48], [51]: 1) the plasma is a nonmagnetized, nonrelativistic, and quasi-neutral fluid; 2) neglect ion diffusion and Hall currents; and 3) the plasma is optically thin. To adequately describe time-dependent, thermodynamic nonequilibrium discharge process and formation of SOPs, the proposed plasma discharge models need to include: 1) a fluid flow model; 2) an electromagnetic field evolution model; and 3) material properties based constitutive model. More specifically, the fluid model consists of a set of transient–advective–diffusive–reactive (TADR) transport equations to describe the conservation law of total mass, mass-average linear momentum, and thermal energy of heavy species and electrons. Based on the assumption that the plasma fluid is nonrelativistic, nonmagnetic, and quasi-neutral, macroscopic Maxwell's equations can describe the electromagnetic field evolution [52], [53]. The final six of fluid–electromagnetic equations with the form "Transient + Advective − Diffusive − Reactive = 0" is summarized in Table I [48]. It should be noted that such a format has an advantage in the formulation of the numerical solver.

Benilov and collaborators have published series papers on multiple solutions in thermionic cathodes [49], [50], [54], [55]. Generally speaking, their approach follows the treatment of self-organization in the systematic framework of bistable nonlinear dissipative systems with computational stability/bifurcation analysis. It was pointed out that in numerical modeling of transport in cathodes of DC glow and arc discharges, bifurcations need to be properly analyzed in order to better understand numerical results and the essential physics. Two key points should be stressed in their approach: 1) given the same discharge current, multiple solutions should exist in the self-consistent theoretical models so that a spotless mode and modes with patterns can be captured and 2) strong positive feedback is required. It represents the characteristic feature of the bistable system. The near-cathode space-charge sheath (sometimes referred to cathode sheath instability) as a basic mechanism can fulfill the criterion.

Pattern formation is generally found in processes over electrodes, including parallel plates and thin slits. SOPs at electrodes are distinctly different at the anodes and the cathodes.

TABLE I

EQUATIONS COMPRISING THE NONEQUILIBRIUM THERMODYNAMIC ARC DISCHARGE MODEL (REPRODUCED FROM [48])

Equation	Var.	Transient	Advective	Diffusive	Reactive
(E1) Total mass	p	$\partial_t \rho$	$\mathbf{u} \cdot \nabla\rho + \rho\nabla \cdot \mathbf{u}$	0	0
(E2) Momentum	$\mathbf{u}$	$\rho\partial_t \mathbf{u}$	$\rho\mathbf{u} \cdot \nabla\mathbf{u} + \nabla p$	$\nabla \cdot \mu(\nabla\mathbf{u} + \nabla\mathbf{u}^T - \frac{2}{3}(\nabla \cdot \mathbf{u})\boldsymbol{\delta})$	$\mathbf{J}_q \times \mathbf{B}$
(E3) Energy heavy-species	Th	$\rho\partial_t h_h$	$\rho\mathbf{u} \cdot \nabla h_h$	$\nabla \cdot (\kappa_h \nabla T_h - \sum_{s \neq e} h_s \mathbf{J}_s)$	$D_t p_h + K_{eh}(T_e - T_h) - \boldsymbol{\tau} : \nabla\mathbf{u}$
(E4) Energy electrons	Te	$\rho\partial_t h_e$	$\rho\mathbf{u} \cdot \nabla h_e$	$\nabla \cdot (\kappa_e \nabla T_e - h_e \mathbf{J}_e)$	$D_t p_e - K_{eh}(T_e - T_h) + \mathbf{J}_q \cdot (\mathbf{E} + \mathbf{u} \times \mathbf{B}) - 4\pi\varepsilon_r$
(E5) Charge conservation	ϕ_p	0	0	$\nabla \cdot \sigma(\nabla\phi_p - \mathbf{u} \times \nabla \times \mathbf{A})$	0
(E6) Magnetic induction	$\mathbf{A}$	$\partial_t \mathbf{A}$	$\nabla\phi_p - \mathbf{u} \times \nabla \times \mathbf{A}$	$(\mu_0\sigma)^{-1}\nabla^2\mathbf{A}$	$\mathbf{0}$

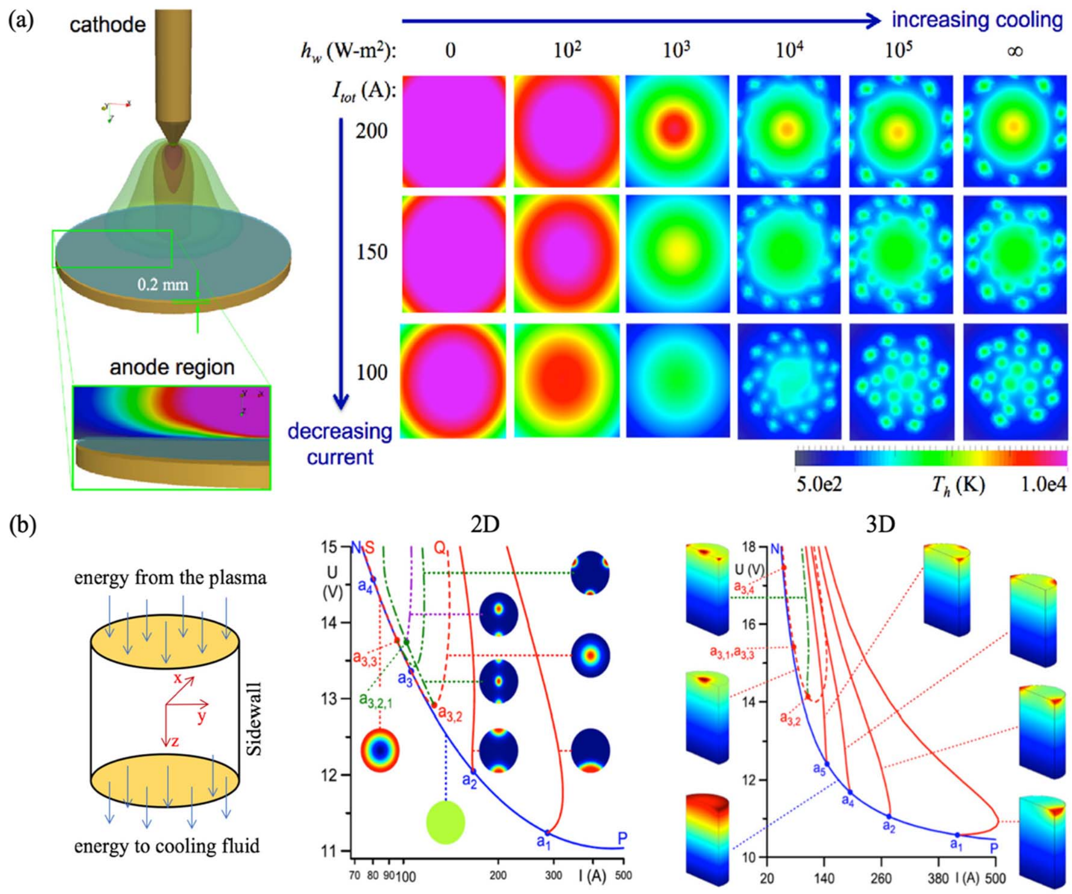

Fig. 4. (a) Anode patterns in the free-burning arc: isosurfaces depicting the 3-D solution (left-top), close-up of the region near the anode (left-bottom), and the effect of total current and degree of anode cooling on anode patterns (right) (reproduced from [4]). (b) Solutions in cathodic arc discharges: schematic of the model, 2-D solutions, and 3-D solutions (reproduced from [49] and [50]).

Fig. 4 shows the simulation results of the anode pattern by FEM in the free burning arc by solving the plasma flow model and multiple solutions in cathodic arc discharges with stability/bifurcation analysis. Fig. 4(a) shows the effect of the total current and degree of anode cooling on SOP in the free-burning arc. Left-top of Fig. 4(a) shows that the arc 3-D view is given by isosurfaces of heavy species temperature, while the left-bottom of Fig. 4(a) depicts the region near the plane and the anode where the SOPs are extracted. The results elucidate that there is a major attachment spot in the middle of the small attachment spots at higher total current and cooling degree. When the total current is 200 A, the anode pattern transition from axisymmetric diffuse to a dominant central spot pattern with surrounding with a set of smaller spots/planetary. With the increase of cooling, the pattern becomes more accentuated. The transition associated with a bifurcation event occurs for a value of $h_w \sim 10^3$–10^4 W·m^{-2}·K^{-1}. This range of h_w is discovered for the total current 100 and 150 A in the transitions. However, the SOPs evolve from planetary and axisymmetric to asymmetrical at 150 A with an increasing h_w. Moreover, the patterns appear small spots in an asymmetric arrangement of for 100 A and high cooling levels. These computational results show that anode spots initiate at the arc fringes, which agree with conclusions reported by Yang and Heberlein [56] from experimental observations and stability analyses.

Fig. 4(b) represents the multiple steady-state solutions of plasma–cathode interaction in cathodic arc discharges in the geometric setup shown on the left. This idealized geometry admits 1-D current density–voltage characteristic (CDVC) solution marked by a blue NP line (middle panel for 2-D). With an account of the effect of the lateral wall, the blue NP line represents the fundamental-mode solution (right panel for 3-D). They both correspond to the uniform solution (also called spotless mode), which is considered as the cold arc portion [57]. Typical representations of current density distribution over the cathode surface (2-D) and over the surface of a cylindrical arc cathode (3-D) associated with each solution are illustrated, indicating the richness of phenomenological aspects in processes of pattern formation over arc discharge cathodes. It should be noted that the 2-D solutions and 3-D solutions are obtained by a zero-gradient boundary condition over the sidewall boundary and allowing heat conduction through the sidewall, respectively. Multidimensional solutions of the n generation branching off from the $n-1$ dimensional solutions at different bifurcation points are also shown. These results demonstrate that stability/bifurcation analysis helps us better understand the distinct features of patterns of steady-state modes and their stability. These cathode models can be applied to the melting/evaporation of cathode material, which may affect the SOPs. The simulation investigations agree with the experimental observation and indicate that evaporation of cathode induces increasing electrical conductivity in anode region [58]. The above computational investigations of new solutions have proved relevant for industrial applications and could be employed to assist cathode design.

IV. SOP Plasma-Activated Liquids

SOP plasma is one type of cold atmospheric plasma (CAP). The difference for common plasma-activated medium (PAM) from the PAM with SOPs is that SOPs form at the interface. The special difference may be that SOP plasma is capable of efficiently controlling the ROS/RNS concentrations in the therapeutical media, and in particular, the ROS/RNS ratios not achievable by other types of discharges could be obtained [24]. The efficiency of plasma-activated liquid or plasma on agricultural and biomedical applications depends on ROS/RNS generation [41], [60]–[63]. Many ways have been devised to detect free radicals and their derived oxidants with different levels of accuracy and sensitivity [64]. These include chemiluminescent assays, chemical assays, fluorescence detection, chemiluminigenic probes, electron paramagnetic resonance (EPR) spectroscopy, and colorimetric (Griess reaction) and related methods [65]–[69]. EPR spectroscopy can directly detect reactive species, while other assays enable being informative if employed with proper controls. The effect of SOP plasma-activated liquids on plants or other biological objects, microbial, viral, and cancer cells is in the same way as plasma-activated liquids with any patterns. Different

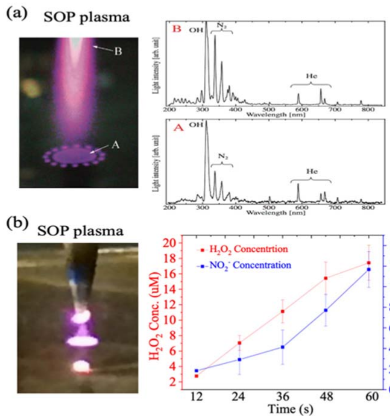

Fig. 5. (a) SOPs appeared on the electrolyte anode surface and OES from 1% Na_2SO_4 solution anode (reproduced from [59]). (b) Image of the SOPs above the DI water: H_2O_2 and NO_2^- concentration of in liquid after SOP plasma treatment with different time (reproduced from [24]).

plasma devices are able to generate SOPs, including pin-water glow discharge setups, gas feeding microdischarge devices, and DBD-like devices [39], [70], [71]. Fig. 5(a) shows the spectrum distribution of SOPs using the 1% Na_2SO_4 solution. The radial distribution of nitrogen lines intensities had a diffused shape involving that for the He atomic line, peaking at the nozzle axis. The anode spot region emission is the same as that of the PC. OH emission and N_2 second-positive system ($C^3\Pi_u$–$B^3\Pi_g$) are mainly emissions. NO lines are weak emission bands in the 250–300 nm wavelength range [72]. The range of 500 and 750 nm is detected as helium bands. ROS/RNS could be defined between 250- and 425-nm bands. Shirai *et al*. [42] indicate that a difference appears in the NG region spectra when the electrolyte was the cathode.

Plasma-activated water (PAW) can be obtained in two modes: plasma discharge above the water surface and plasma discharge in water. Plasma discharge in water has lower energy efficiency comparing with the above water surface [73]. Plasma discharges over liquid surfaces, and resulting in reactive oxygen species/reactive nitrogen species (ROS/RNS) transferring from the gas phase to the liquid [74]. For SOP plasma, plasma-treated liquids (such as PAW) are obtained from SOP plasma forming over the liquid's surface. Fig. 5(b) shows the ROS/RNS contents in the self-organization glow discharge-treated DI water. The concentration of H_2O_2 and NO_2^- increase with the treatment time [75], [76]: possible reactions about H_2O_2 and NO_2^- formation in plasma-treated liquid are listed in [77]. On the other hand, scientists also proposed potential chemical and physical processes taking place at the plasma–liquid interface [78], as shown in Fig. 6. These processes contain gas multiphase species transport, phase chemistry, interfacial reactions, mass and heat transfer, and liquid phase chemistry. At the plasma–liquid interface, temperature gradients are characterized, and it still needs to determine whether a real connection between plasma at liquid water and a supercritical temperature occurs. There is a distinction between the interfacial region and the bulk liquid. The interfacial region is the location related to the major processes of short-lived species occurring. Some reactive species, such as O atoms, OH radicals, and OOH radicals, penetrate the

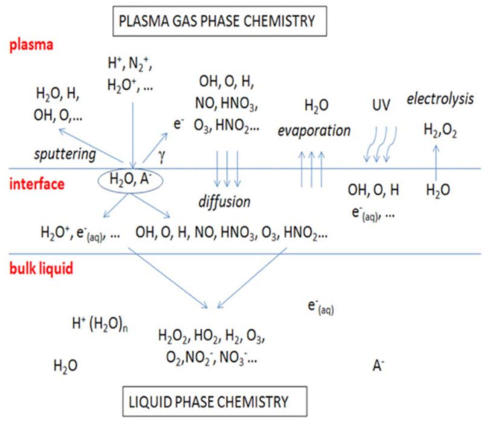

Fig. 6. Important processes of reactive species transferring at the plasma–liquid interface (reproduced from [82]).

interfacial region into the bulk liquid and interact with it [79], [80]. The interfacial layer thickness will change because radicals have different depths of penetration based on their lifetimes. Finally, plasma species into liquids become plasma solutions including ROS/RNS [81]. Generally, ROS/RNS plays a major role in plasma agriculture, food safety, and plasma medicine, such as replacing the traditional sanitizing solution applied for disinfection, applying for seeds/crops as fertilizer, and using as an anticancer, antimicrobial, and dental treatment agent. We will discuss the potential applications of SOP plasma activating liquids for agriculture, food safety, and biomedicine in the following next two sections.

V. Potential Agricultural Applications of SOP Plasma-Activated Liquids

According to the State of Food Security and Nutrition in the World 2019, world hunger has slowly been on the rise since 2015 after decades of steady decline. There are approximately 821 million people suffering from hunger around the world in 2018. By 2050, the population will reach 10 billion on earth, which urgently requires innovative approaches for agriculture and food production. It highly challenges to produce lots of foods with safety and high quality during food production due to emerging pathogens. Cold plasma has great potential in several applications of food industry: microbial disinfection, starch modification, improving rice cooking quality, enzymatic inactivation, and enhancing germination of seed [83]–[85]. For example, enzymes like peroxidases and polyphenol oxidases involving enzymatic browning reactions induce the loss of nutritional quality, while enzymes like lipoxygenase, lipases, and pectin methylesterase result into a detrimental effect on the food organoleptic quality [86], [87]. Plasma-treated liquid has the ability to kill a large panel of germs and deactivate microorganisms that otherwise cannot be disinfected by gas plasma [88], [89]. SOP plasma-treated liquids, containing mainly ROS and RNS, can be an alternative method for sterilization of foods and fertilizers for crops and seeds.

Fig. 7(a) illustrates the effect of PAW on the development of the root system of Zinnia annual spears. The groundwater treated by plasma yields a 15%–20% increase of the degree

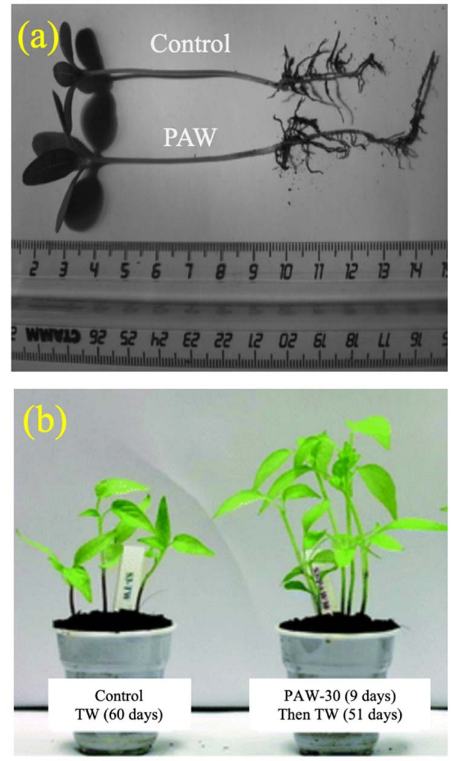

Fig. 7. (a) Effect of PAW on the development of the root system of Zinnia annual spears (reproduced from [103]). (b) Long-term effect of PAW on pepper crops. PAW-30: DI water treated by plasma for 30 min and TW: tap water (reproduced from [96]).

of the culture's germinability and a 1.5- to 2-fold increase in the plant roots' length comparing with the control specimens. PAW-treated seeds increase eventual yield, which could be partially (at least) involving antimicrobial and antifungal [90]. It has to clear up the role of the biological factors and surface chemistry in enhancing the yield: the permeability of O_2 and CO_2 in PAW is essential for germination [91]–[93]. PAW can be used as a potential method for pretreatment of seeds to increase yield and control the germination speed. PAW-treated seeds with high hydrophilicity might save a lot of water necessary for irrigation [94], [95]. Fig. 7(b) shows the effect of PAW on pepper plant growth and healthier leaves. The efficiency of seeds germination depends on the PAW treatment time, that is the amount of hydrogen peroxide (H_2O_2) and nitrate (NO_3^-) produced in the water [96]. Also, the retention of seeds nutritional characteristics is important, and reactive species in PAW can cause important changes in grains' physicochemical constituents. Applying PAW to the food and agriculture has the potential to increase food quality and safety [97], [98]. It can efficiently degrade pesticides/mycotoxins, reduce food waste, and inactivate pests, which also can be used to generate nitrate-rich substrates as fertilizer [60], [99]. In PAW treatment process, lipid/starch oxidation and protein modification can occur through multiple chemical reactions [100]. Lots of DBD reactors are utilized for the treatment of liquids: the plasma easily forms SOPs at the liquid interface and the radicals diffuse in depth to obtain plasma solution for agriculture and food processing [101], [102]. SOP plasma or SOP plasma-treated liquids for the food and agriculture continuum potentially increase food quality and safety, which can efficiently inactivate pests as well as degrade pesticides/mycotoxins. SOP plasma-treated liquids can be employed to produce rich substrates' nitrate, thus increasing seeds yield and germination.

The efficiency of inactivation depends on PAW treatment time [104], [105]. The PAW electrical conductivity increases linearly with the plasma treatment time, and the pH quickly drops in the first 10-min treatment and reached around 3 with a steady-state after 20-min treatment [106]. Many scientists also speculated that reactive species and acidity in PAW were interconnected. Lower pH helps ROS/RNS to penetrate cell walls, and ROS/RNS decreases the resistance of bacteria to acidic environment [107]. Active ions generating in the PAW were various ROS/RNS [108]–[111]. ROS, as the most important agents, generate in the inactivation process, which is long- and short-lived species. On the other hand, PAW containing complex chemical compounds can create other species with a lethal effect [112]. For example, the synergistic combination of H_2O_2 and NO_3^- has an antibacterial function. Choi *et al.* [113] compared PAW with sodium hypochlorite and tap water (TW) on killing foodborne pathogens, inactivation of background microbiota, and shredded salted Chinese cabbages' quality. PAW shows a significant reduction in lactic acid bacteria, mesophilic aerobic bacteria, coliforms, yeast, and molds. In addition, to compare with the antibacterial efficiency of PAW, Qian *et al.* investigated plasma-treated lactic acid (PALA) affecting beef quality and Salmonella Enteritidis [115]. The PALA antibacterial activity is closely involving the synergistic effect of H_2O_2 and NO_2^-, and there was no negative effect on beef quality (similar to PAW).

Fig. 8 shows the potentials mechanisms for the disinfection of PAW. The pH is related to the ROS/RNS and largely depends on the feed gas, treatment time, and treatment distance [114]. Most of the bacteria are significantly affected the environmental pH due to no mechanism to change their internal pH. The mechanisms of UV radiations and shock waves in PAW are the thymine bases' dimerization in DNA strands and the creation of cavitation bubbles, respectively [116]. Major ROS in PAW, including H_2O_2, hydroxyl radical ($_*$OH), and ozone (O_3), is evaluated as potent antimicrobial agents [117], [118]. The $_*$OH starts the peroxidation reaction of lipid through subtracting H from the unsaturated carbon bonds of fatty acids resulting in the end product: malondialdehyde, which damages DNA and induces cell death [119], [120]. Generally, the transport of H_2O_2 and O_3 from the PAW into the microbial cells induces the internal injure via the destruction of proteins, and breakdown of DNA and other internal components. One more H_2O_2 antimicrobial mechanism is to generate intracellular $_*$OH causing oxidative damage of DNA [121], [122]. The major RNS in PAW, including nitrates, nitric oxide (NO), nitrites, and peroxynitrites ($ONOO^-$), lower the pH and form strong oxidizer ($ONOO^-$) for microbial disinfection [123]. Moreover, the combination of physical parameters and RNS/ROS can have a synergistic effect. The oxidation–reduction potential also plays an important role in the microbial inactivation, damaging the cell membrane and defense mechanism [124]. Four potential mechanisms are driven by PAW treatment and

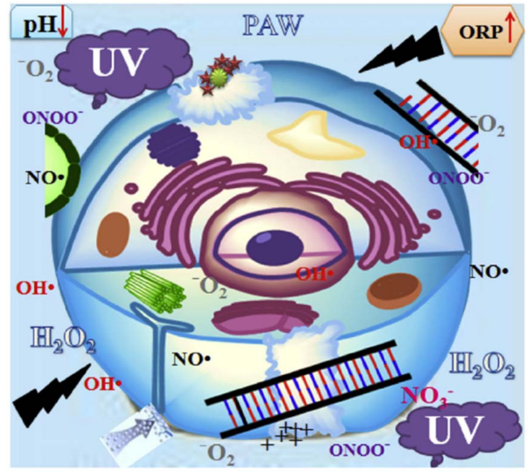

Fig. 8. Schematic of the PAW causing cell death through different mechanisms: lipid peroxidation, ROS/RNS, electroporation (+), and physical parameters (reproduced from [125]).

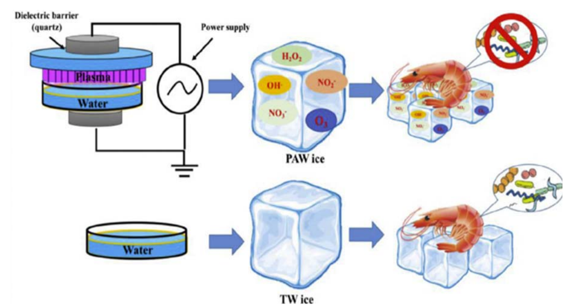

Fig. 9. Application of PAW (generated by DBD) ice for shrimp preservation (reproduced from [130]).

contribute to bacterial cell death, containing damaging cell membranes, etching cell walls, destruction of genetic material, and protein/enzyme denaturation.

Seafood, rich in lipids and proteins, has limited shelf-life and easily loses its quality due to the activity of spoilage microbes and endogenous enzymes [126]. PAW ice provides an alternative storage technology for the food industry. Fig. 9 shows the application of PAW (generated by DBD) ice for storage of shrimps, and PAW ice efficiently inhibit the microorganism growth, and stops losing freshness shrimp and quality, inducing longer shelf life. *Aspergillus spp.* are generally considered as "storage" contaminants and their growth is involving inefficient drying [127]. The overall effects of PAW on *Aspergillus spp.* significantly decrease the remaining counts and subsequently induce cell leakage. Meanwhile, Ma *et al.* [128] demonstrated that PAW could kill *S. aureus* inoculated on strawberries without causing a significant change in pH, firmness, and color. During six-day storage after PAW treatment, there is almost no visual fungal spoilage on the strawberries. Cebrián *et al.* [129] also proposed that *S. aureus* developed stress resistance responses after exposure to sublethal environmental stress, inducing homologous stress resistance increased via causing a program of protein synthesis and gene expression.

Plasma-treated buffer, containing ROS and RNS, is an effective and safe antimicrobial agent against pathogenic bacteria of

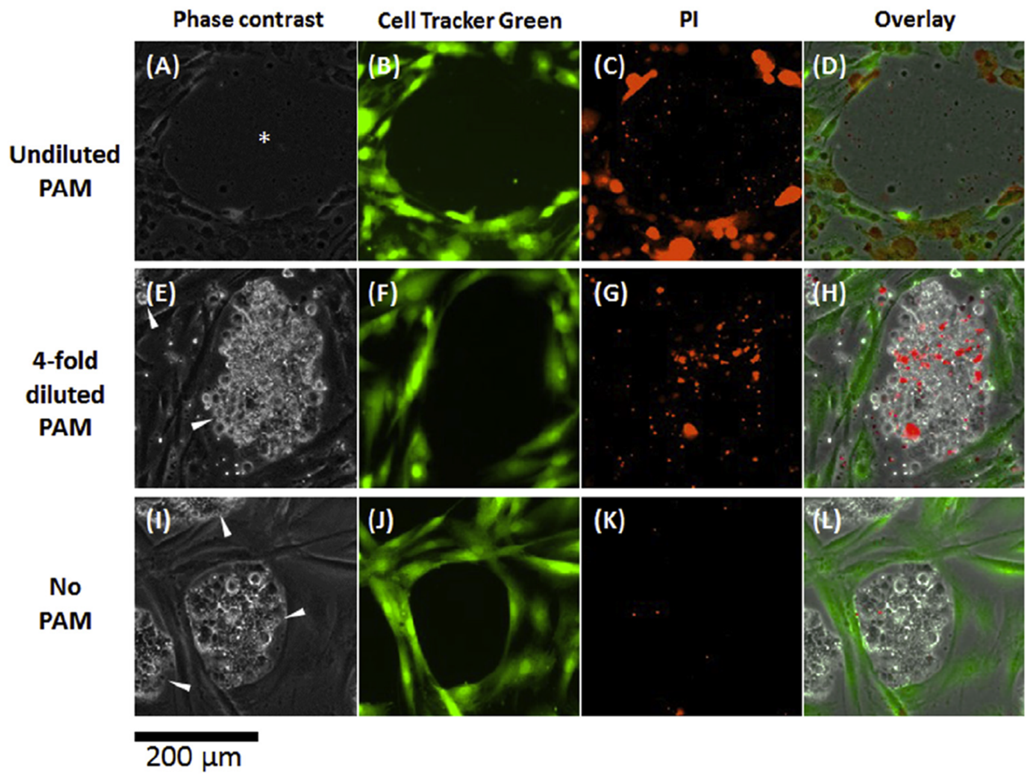

Fig. 10. Effects of PAM on differentiated cells NHDFs and undifferentiated 201B7 hiPSCs. Cells treated with (A)–(D) undiluted PAM, (E)–(H) fourfold diluted PAM, and (I)–(L) without PAM. (A) Asterisk indicates the hiPSCs attachment before PAM treatment. (E) and (I) Arrowheads indicate hiPSCs (reproduced from [147]).

plant and has a wide range of applications to enhance the shelf life of stored food and crop production [131]. Chen *et al.* [132] studied the effects of PAW on antioxidant activity, quality maintenance, and the native microflora survival of fresh-cut pears, indicating that PAW highly prohibited the growth of aerobic bacteria, mold, and yeast during storage. There is no significant change in the titratable acidy and soluble solid content. Gavahian *et al.* [133] investigated PAW affecting visual quality and the textural of shiitake mushrooms. After stored for 1 week, PAW treatment enhances the postharvest quality and limits textural changes and undesirable color. Thus, the above results provide significant insight into developing and applying PAW to improve the quality of products and microbiological safety in the food industry. The potential applications of PAW in agriculture and food are extensive, including sterilization of seeds, enhancing seed germination and yield, removal of volatile organic compounds, postharvest sanitation, fertilizer, reducing pathogen invasion, disinfection of products prior to packaging, control of pests and pathogens during retail storage and display, sterilization of food processing equipment, and others [134]–[138].

VI. Potential Biomedical Applications of SOP Plasma-Activated Liquids

Cold plasma can be employed for biomedical applications because plasma is generated at room temperature and atmospheric pressure containing ROS and RNS [139], [140]. ROS and RNS promoting cell proliferation or cell death depend on the dosage. Extreme dosage of ROS induces

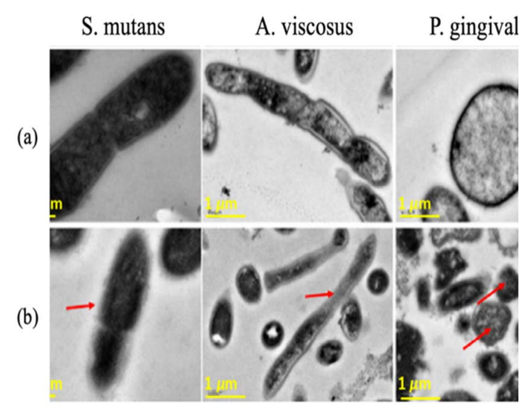

Fig. 11. TEM images of *P. gingivalis*, *A. viscosus*, and *S. mutans* (a) before and (b) after PAW treatment. Red arrows show the change of surface morphology after treatment of PAW (reproduced from [157]).

damage of proteins, DNA, senescence, lipids, and induce apoptosis [141], [142]. Recently, the plasma-treated liquid is one of the important plasma medicine tools and has been widely investigated for many biomedical applications, such as cancer therapy, microbial disinfection, regenerative medicine, and dental treatment [143]. Plasma-treated liquid, stable at room temperature, is unique because it can generate ROS/RNS inside tissues without harming healthy tissue. There are many factors affecting the efficacy of plasma-treated liquid, such as treatment time, storage duration, air gap, power, and storage temperature. A discussion of plasma-treated liquid for regenerative medicine, microbial disinfection, dental, and cancer therapy as follows.

Human-induced pluripotent stem cell (hiPSCs), as one of the human pluripotent stem cells, is potential sources for cell transplantation therapy, drug screening, and regenerative medicine [144], [145]. Japanese RIKEN Center performed the first human trial of hiPSCs-derived retinal pigment epithelium in 2014 [146]. Matsumoto *et al.* [147] investigated PAM on hiPSCs and indicated PAM selectively killing hiPSCs and no toxic effects on differentiated cells (Fig. 10). Till now, studies characterized PAM affecting differentiated normal cells and indicated that less harmful effects were exerted by PAM on these cells. PAM has some following advantages [148], [149]: 1) easy and cheap to use; 2) elimination ability; and 3) no or minimal antigenicity. Tanaka *et al.* [150] showed the effect of PAM on normal astrocytes and glioblastoma cells, and pointed out that glioblastoma cells were killed by PAM via PI3K/PTEN pathway without damage of normal astrocytes. Torii *et al.* [151] showed similar results that gastric cancer cells are less resistant to PAM than WI-38 human fibroblasts. PAM can be clinically applied for regenerative medicine to eliminate potentially tumorigenic undifferentiated hiPSCs from a number of differentiated cells before transplantation.

Plasma-treated liquids are also employed as antiviral and medical disinfectants. Disinfection of hazardous microorganisms is unusually impotent for environmental safety, which is an important topic for public health and the economy. Zhang *et al.* [152] explored the sterilization efficiency of PAW against *S. aureus*. PAW treatments reduced *S. aureus*, and its sterilization efficacy depended on the concentration and treatment time. The integrity of membrane potential, cell membrane, and DNA structure, and intracellular pH homeostasis were damaged. Newcastle disease is an infectious viral disease and induces serious economic losses to poultry industries and domestic animals, which also has mild effects on humans [153]. Su *et al.* [154] studied the effect of plasma-treated solutions on the Newcastle disease virus. The possible mechanism of plasma-treated solutions' inactivation of Newcastle virus is ROS/RNS. ROS/RNS might degrade viral protein, destroy RNA structure, and change viral morphology, finally inducing virus inactivation [155]. The plasma-treated liquid is a promising environmentally friendly and chemical-free disinfectant for medical and industrial applications due to resolving the issues of environmental sanitation and public health. Also, plasma-treated liquids can be employed for the sterilization of medical equipment and dental, which are very cost effective and safe. Caries and periodontal diseases are the main factors inducing tooth loss and global oral health issues according to The World Health Organization (WHO) [156]. Li *et al.* [157] explored the antimicrobial effect of PAW mouthwash and elucidated that the morphology of normal cells was changed by PAW treatment, as shown in Fig. 11. This suggests that PAW could be a novel mouthwash with antimicrobial functions. Ye *et al.* [158] also investigated PAW-treated three oral pathogens: *S. mutans*, *P. gingivalis*, and *A. viscosus*. They indicate that PAW is a novel and promising antimicrobial mouthwash to treat periodontal related diseases and dental caries.

One of the important SOP plasma-treated liquid applications is for cancer therapy [159]–[165]. Over 100 types of cancers affect humans, and about 90.5 million people had cancer in 2015 [166]. Undoubtedly, cancer is a paramount important problem, thus sophisticated development approaches are urgent needs to meet these challenges. Different treatments containing medication drugs, radiation-based approaches, and surgical techniques are employed for cancer treatment. However, more progress is demanded to solve this stubborn problem and reduce drastically the mortality rate. Plasma-based cancer therapy is considered as the novel technique exhibiting a huge potential in treatment cancers [167]–[174]. Fig. 12(a) shows plasma with SOPs treating SSs employed human normal cells line H6c7 and human cancer cells line BxPC-3. SOP plasma-treating SS had an effect on the selective manner of normal and cancerous pancreatic cells. The trend of cancer and normal pancreatic cells might be related to the trend of RNS and ROS concentration. H_2O_2 reacts with NO_2^- to form peroxynitrite $OONO^-$ and H_2O [175]. $ONOO^-$ is commonly considered as a nitrating agent and powerful oxidant that damaging to cancer cells [176]. Thus, the combination of ROS and RNS in plasma solution plays a synergistic effect on apoptosis [177], [178]. Freund *et al.* [179] also investigated physical plasma-treated SSs employed to CT26 colon cancer cells and indicated this treatment promoted an immunogenic phenotype.

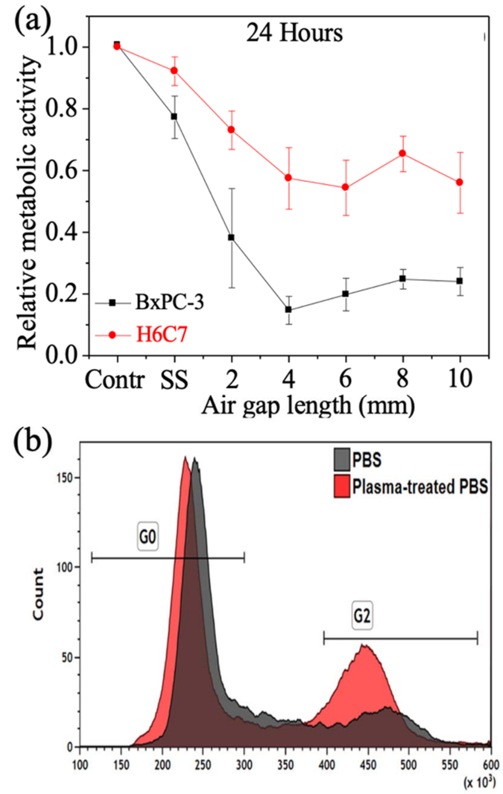

Fig. 12. (a) Effects of RPMI/KSFM, SS, and five plasma-treated SSs at 2-, 4-, 6-, 8-, and 10-mm air-gap length for 40-s duration on the viability of the H6c7 (human pancreas normal cells) and the BxPC-3 (human pancreas cancer cells) after 24-h incubation, respectively (reproduced from [25]). (b) Plasma-treated SS caused CT26 cells' morphological phenotype (reproduced from [179]).

Fig. 12(b) exhibits that flow cytometry of DNA content, which shows that the amount of chromatin in the proportion of cells significantly increased twice in both groups. Cell cycle

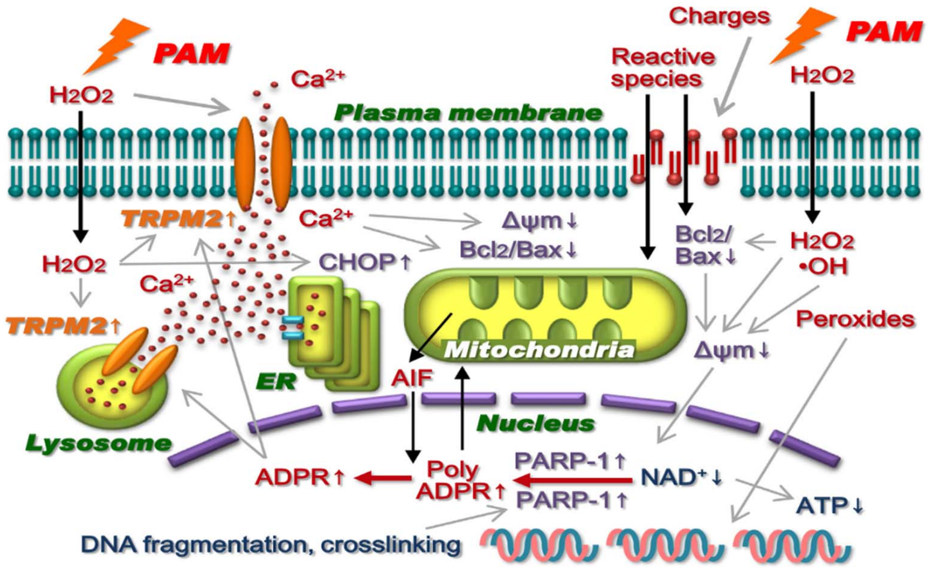

Fig. 13. Signaling mechanism for reactive species in PAM causing cell injury (reproduced from [148]).

arrest involving toxic stimuli is not special for malignant cells, generally considering as many chemotherapeutics' side effects in cancer patients [180]–[182]. Plasma-treated SS treatment leads to largely increasing calreticulin (CRT) in colon cancer cells, which is an important marker for immunogenic cell death (ICD) and the chaperon came from the endoplasmic reticulum (ER) translocating to the surface of the cell serving as an eat-me signal for tumor material phagocytosis [183]–[185]. DAMPs32 (Damage-associated molecular patterns), for example, HMGB1 (high-mobility-group-protein B1) and HSP70 (heat-shock protein 70), increased the surface of tumor cell after treatment of plasma-treated SS. Here, HSP70 is able to cause DC maturation [186]. HMGB1 is able to bind to several receptors like Tim3, RAGE, TLR4, and TLR2, and which are immunogenic signaling cascades [186]. These induce maturation of suppression of regulatory T-cells (Tregs), DC-dependent priming of T-cells, and dendritic cells (DCs) [187], [188]. Therefore, the plasma-treated SS is cytotoxic to the murine cancer cell lines PDA6606, MC38, and CT26, which raises a proimmunogenic phenotype. Tanaka *et al.* [189] clinically employed plasma-activated lactate (PAL) and indicated that PAL reduced tumor volumes. No side effects are noticed in the mice, suggesting PAL effective and safe. In addition, double-distilled PAW is effective to kill cancer cells, while it is suggested to employ in the clinical setting because of unfavorable osmolality. Storage of plasma-treated liquid will not lose the major oxidant H_2O_2 in the solution [190]. Numerous studies have reported cytotoxic activities of the plasma-treated cultured medium in various cancer therapy both *in vitro* and *in vivo* [33], [35], [191]–[200]. It should be pointed out that the immediate concentration of H_2O_2 in plasma-treated liquid does not depend on its protein content, indicating pretty slow decay [201]–[203]. Thus, plasma-treated saline is able to be frozen and stored for a long time, which should be further characterized for clinical cancer therapy in the future.

ROS and RNS in plasma-treated medium have been proposed for cancer therapy with a selective manner [204]. ROS is a cytotoxic agent (considered as the main mediator of plasma cytotoxicity) and inhibits cell growth at a lower concentration than commercially supplemented H_2O_2 cultures [205]–[208]. Other cytotoxic components in the plasma-treated solutions increased with plasma treatment time in line with H_2O_2 [209]. The RNS in the plasma-treated solutions has been reported to be the reason for synergistic antimicrobial effects and might also be a response to enhanced cytotoxicity [112], [210]. Reactive species in plasma increase intracellular ROS: cytokine release or cell proliferation increasing at low concentration; causing cell cycle arrest and triggering apoptosis at and higher concentration [211]–[216]. Plasma-causing apoptosis by generation of intracellular ROS is considered as the promising therapy pathway for tumor treatment, while it also brings the risks of inducing epigenetic alterations and oxidative stress-induced genetic involvement in carcinogenesis [217]–[220].

Fig. 13 shows a signaling mechanism for H_2O_2 produced by PAM-induced cell injury. ROS inducing DNA nicks' reaction activates PARP-1 and brings the cleavage of NAD^+ into ADP-ribose and nicotinamide to form a number of polyADPR. It results in depletion of ATP and the consumption of NAD^+. PolyADPR can mediate AIF release and translocate to the mitochondria. The AIF translocation released from the mitochondria to the nucleus triggers large-scale nuclear injury and chromatin condensation [221]. $\Delta\psi$m reduction increases the mitochondrial membrane permeabilization and allows the AIF efflux, which has been determined as a caspase-independent pathway of apoptosis [222]. H_2O_2 might disturb the mitochondrial–nuclear network through decreasing $\Delta\psi$m, reducing the Bcl_2/Bax expression ratio, depleting NAD^+, releasing AIF, and activating PARP-1. The product of extracellular/intracellular H_2O_2 is ADPR accumulation activating TRPM2, which induces Ca_2^+ extracellular influx and releases from intracellular stores. Membrane damages by H_2O_2 induce apoptosis; meanwhile, it might increase membrane permeability for extracellular reactive species. Many articles have published to explain ROS-triggered apoptosis through caspase-independent pathways [150], [223]–[227]. In addition, PAM generated in a close DBD system exhibits a reduction in proliferation in the tumor model and an increase in ATP release and CRT exposure [35]. PAM shows the potential applications inducing ICD through activation of the innate immune system. PAM can be used as oral medication or injected into the blood for cancer therapy [142]. Moreover, the effectiveness of plasma-treated media/liquids increases the potential for clinical applications of cancer therapy because it can be prepared in advance and stored until use [228].

Conclusion

This review clearly demonstrates computational/experimental results on the formation of the SOP in cold plasma. The computational and theoretical analysis explore more comprehensive plasma models, which are appropriate to capture the processes of SOP formation in plasma at the industrial level. There are many approaches to control SOP processes, either by suppressing or enhancing, including gas flow, gas species, gap length, electrolyte conductivity, and driving current. SOP plasma can activate various liquids, such as water, ringer's solution, SS, cultured medium, and FBS. In addition, convincing evidence of SOP plasma toward potential applications of agriculture and biomedicine has been accumulated. The fundamentals of the plasma-treated liquids properties and their actions for agricultural and biomedical applications were discussed. The ROS and RNS formation in plasma-treated liquids and their interactions cell membrane, nucleic and internal proteins are responsible for their application efficiency. It is clear that plasma-treated liquids appear to be useful, powerful, and safe tools for seed germination, plant growth, food safety, regenerative medicine, sterilization, dental diseases, cancer therapy, and plasma immunotherapy.

Although plasma-treated liquids have a number of significant advances, many questions still remain unanswered. The complexity of SOP plasma devices, such as different design and operation parameters, can produce various compounds under different mechanisms. The important limitation is the short-lived radicals generated in the plasma-treated liquids. For plasma–liquid interactions, more research related to ROS/RNS and their reactions is required to elucidate the biological effect caused by plasma-treated liquids. Scientists will pay more attention to determining the effects of plasma-treated different types of liquid solutions other than medium or water. Advanced computational methods and tools will be employed to predict chemical compounds generation or synthesis in plasma-treated liquid solutions through governing solution dilutions or reactive species. Future research will focus on investigating plasma-treated liquids' antibacterial effect on other fresh products and bacterial strains, determining foods' chemical changes and nutrition, enhancing the efficiency of inactivation, as well as developing large-scale industrial plasma device. Moreover, the safe administration routes of plasma-treated various liquids have not been established for humans yet; thus, pharmacodynamic and pharmacokinetic data are required to make plasma solution treatment more practical. In the end, more detailed research on plasma-treated liquids for a sustainable tomorrow, involving seed germination, plant growth, food safety, regenerative medicine, sterilization, dental diseases, and cancer therapy, is required to confirm their safe and potential applications.

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