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Review Article

Others Section

Biomedical Applications of Cold Plasma

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ABSTRACT

Plasma medicine is branch that employs Cold Atmospheric Plasma (CAP) as a potent tool for biomedical applications. CAP produces high-level reactivity (free radicals, electrons) and can be generated by noble gases. CAP is rich in Reactive Nitrogen Species (RNS) and Reactive Oxygen Species (ROS). These ROS and RNS which include Ozone (O_3), Nitrous Oxide (NO), Hydroxyl Radicals (OH), and Nitrogen Dioxide (NO_2), gas particles, charged ions, neutral reactive oxygen which are primarily responsible for decontamination of microbes in various living tissues. Furthermore, CAP only have high excitation energies of electrons as compared to neutrals and ions which makes CAP an excellent tool for application on cells and tissues without any thermal damage. Cold plasma has also been successfully implemented for virus disinfection as its regarded as eco-friendly, efficient and novel technique for decontamination of virus. CAP treatment has also enabled inactivation of virus strain in both plant and animal species without inducing any physiological damage to them. Plasma chemistry essential for inactivation of pathogens is dependent on fine-tuning of various parameters which include plasma supply frequency, gas composition, input energy duration, pulse form, and modulation which has led to development and research of numerous portable plasma devices for different treatment methods in plasma medicine. CAP generated is extensively applied for wide range of biomedical applications including dentistry, microbial disinfection (bacteria, viruses, fungi), treatment of skin diseases, wound treatment, and biofilm treatment.

Keywords: Atmospheric pressure plasma, Disinfection, Plasma medicine, Reactive species, Sterilisation

INTRODUCTION

Plasma medicine comprises of Cold Atmospheric Plasma (CAP) to produce specific amounts of reactive species which are focussed on biological surfaces (tissues/cells). Plasmas have been used for a long time for sterilisation of medical equipment, packaging in the food industry, implants, blood coagulation, dentistry, biofilm treatment [1-6].

Cold atmospheric plasma has been implemented for wide spectrum of applications that include- implant surface treatment, medical equipment sterilisation, microbial disinfection. These applications are possible due to inherent benefits of CAP such as scalability, portability and disinfection effectiveness in small and confined spaces. Currently there are numerous CAP based devices that are employed for treatment of tissues and cells. CAP is implemented for rapid sterilisation. There are also new research possibilities for drugs delivery through tissues and biofilms [7-11]. The results of these specific experiments could translate into plasma based drug delivery techniques [12]. However, this would rely on factors such as conceptual design of plasma sources (whose chemical reactivity could be controlled), application of plasma physically, and most importantly in vivo and in vitro experiments.

The CAP is generated through several mechanisms that include- microwave frequencies, Radiofrequency (RF), high voltage (DC/AC). Since, these CAP are non equilibrium plasmas, they consist of both reactive species (electrons and ions) as well as excited species that has immense potential in plasma based medicine as well as drug delivery [13-17].

Plasma medicine is an evolving field of research that is based fundamentally on plasma physics which governs the physical and chemical properties of CAP. The rapid development of CAP based techniques is attributed to the interdisciplinary nature of this research which encompasses various fields that include physics, chemistry, microbiology and engineering for characterisation, analysis as well application of this CAP technology. This review focusses on the current advancements and research pursued across these domains. Numerous CAP based industrial applications are currently being employed in various engineering processes [18,19]. Even though, there are several existing applications of CAP in biomedical field and few efforts have been made to understand the impact of CAP on biofilms (complex microorganism groups enclosed by glue matrix which further improves resistance towards external stresses) [20]. As the conventional antimicrobial therapy has poor penetration capacity it is not particularly effective against the biofilms which is primarily responsible for inhibiting disease eradication. Also, the conventional antimicrobial therapy several drawbacks like systemic toxicity and bacterial resistance. But when the bactericidal effects of CAP are considered, then it is found that the resistance of bacteria remains the same while being exposed to CAP. These results are clearly suggested that CAP is potent tool for in-vivo treatments [21].

Even though, CAP is generally close to room temperature, yet it contains sufficient chemically reactive gas species utilised for numerous biomedical applications. In this CAP only electron possess high excitation energies as compared to the ions and neutrals. Furthermore, during the CAP generation process these high energy electrons collide with the working gas ($He/Ar/N_2/O_2$) which is used for generating plasma thus resulting in higher ionisation and disassociation levels. As the neutrals and ions are comparatively at a much lesser temperature than electrons in the CAP hence there is no thermal damage. It is imperative to note that this property enables CAP to be implemented for tissues, cells, biological matter, thermally sensitive materials, [22-24].

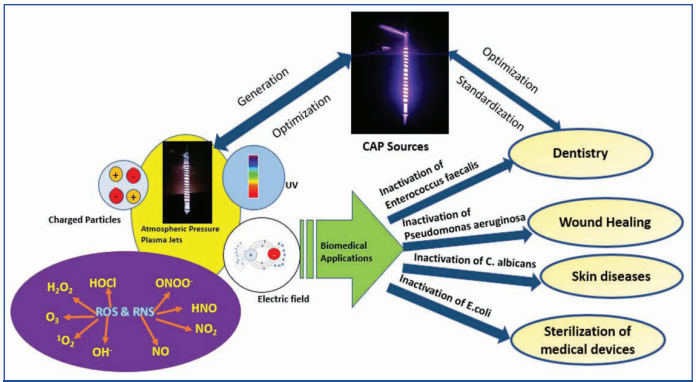
Recently, huge number of CAP devices have been envisaged, designed, developed and implemented for many research related applications. Broadly, these non equilibrium CAP have been classified as indirect and direct discharge [13-17]. Since, various research groups use different CAP based devices for numerous biomedical applications thus making the comparison between them quite complicated. Due to these technical differences of design of various CAP devices developed across globally it becomes imperative to implement a standardised way to comprehend the effectiveness and

security of the CAP devices. For this specific reason, there are many organisations {European Committee for Standardisation (CEN), German Institute of Standardisation (DIN), International Organisation for Standardisation (ISO)} for technical regulation of the CAP device [25]. Some of the CAP devices have already got the approval of United States Food and Drug Administration to for the clinical usage.

The CAP applications have received lot of attention from the medical research community. The biomedical applications of CAP include, viral infection treatment (herpes simplex), wound treatment and skin diseases, implant surface treatment, biofilm treatment etc.

PLASMA MEDICINE

The CAP have been employed in wide spectrum of biomedical applications that are depicted in [Table/Fig-1] (conceptualised by the authors) which includes dental medicine, treatment of skin diseases and wound healing and sterilisation of medical equipment.



[Table/Fig-1]: Biomedical applications of atmospheric pressure cold plasma.

It is essential to perform modelling, simulation and experiment work on these atmospheric pressure plasmas for understanding the chemical and physical mechanisms in detailed manner. Certain important parameters such as seed electrons, photo ionisation effect and impact of electric field can be obtained using fast imaging techniques that have high resolution up to micrometre range and time resolution of up to nanoseconds.

For examining the active components of CAP which include Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), electric fields, and Ultraviolet (UV) radiation, their generation mechanism as well as their interrelationship between them should be examined in detailed manner.

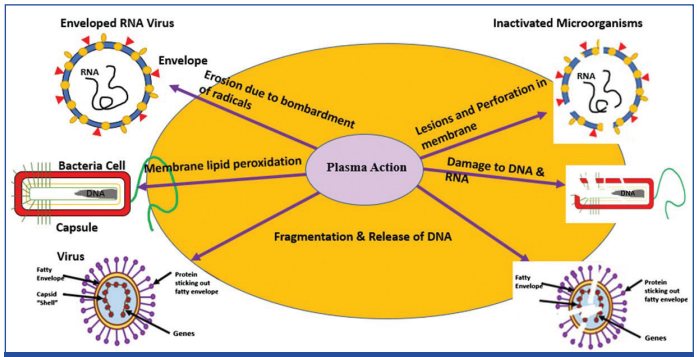
Numerous existing measurement technology are employed for studying CAP which include- optical emission spectroscopy for gas discharges, Rayleigh and Raman for understanding electron parameters, mass spectroscopy, stark spectroscopy. The plasma reactive species generation mechanism could be understood through modelling and simulation of various plasma reactions [26].

When CAP based devices have also been used for bioaerosols and fluids also, thereby plasma interacts with water directly. The lifespan of the bioaerosols relies on the evaporation of water and thereby impacts the plasma chemistry. While implementing CAP for treatment of skin diseases, it essential to adjust the treatment plasma dose accordingly [27]. CAP sources scale from small to large size devices and their design depends on several factors such as surface type of target, electrical parameters for a particular biomedical application (voltage, current, supply frequency, pulse width). The rapid progress in the field of CAP technology is moving towards incorporating it in personalised devices, laptops and other portable devices including those operating on battery.

The implementation of Artificial Intelligence (AI) in plasma diagnostics and mathematical modelling of plasma reactions would lead to rapid progression in commercialisation of CAP based devices with augmented disinfection efficacy [28]. Furthermore, innovative high-strength materials can used as electrode materials, semiconductor based power sources can be used to increase efficiency of CAP devices while also maintaining cheap manufacturing cost.

COLD PLASMA APPLICATIONS- INACTIVATION OF PATHOGENS

Some microorganisms such as viruses, bacteria, and fungi behave as pathogens and trigger diseases. The resistance of these microbes is quite different from each other and can be classified as very susceptible, less resistant, intermediate resistant, highly resistant, and most resistant [29]. The various cold plasma inactivation mechanisms for pathogens are shown in [Table/Fig-2] (conceptualised by the authors).



[Table/Fig-2]: Cold plasma inactivation mechanisms of various pathogens.

Helminth eggs, protozoan oocysts, and bacterial spores fall in category of microorganisms which are highly resistant. The microbes such as fungal spores, protozoan cyst and non enveloped viruses fall in category of intermediate resistant microbes. The type of cold plasma treatment is different for various types of microbes and depends on the resistance of the microbe [30].

Bacterial Inactivation-Cold Plasma

Numerous studies that have explored the advantages of cold plasma in treating highly drug resistant bacteria [30-35]. Various studies have also proved that cold plasma produces Reactive Oxygen and Nitrogen Species (RONS) when using air as working gas [36,37]. The investigation done by Nicol MJ et al., proved that there was about 90% reduction in both gram negative and gram positive strains of bacteria on different surfaces (solid, porous, liquid) [38]. Furthermore, these experiments demonstrated the generation of RONS during cold plasma treatment is essential for inactivation of bacteria.

The diverse benefits of CAP which include portability, scalability and efficacy of the technology has resulted in numerous microbial disinfection-based applications. As this cold plasma is generated at room temperature hence can be applied to biomaterials without any thermal damage. Another benefit of CAP treatment it's not dependent on liquid chemicals and relies on dry chemistry. Furthermore, results of numerous investigations have proved that bacterial growth has not taken place after CAP treatment [39-41]. CAP treatment has been extensively applied for inactivating bacteria in biofilms is dependent on bacterial cell wall thickness. Few studies also suggested the efficacy variation of CAP treatment for gram negative and gram positive bacteria due to their cell thickness difference [40-42]. The experimental results of Mai-Prochnow A et al., showed that gram negative bacteria (*Pseudomonas aeruginosa*) having cell thickness of 2.4 nm was completely inactivated using CAP treatment whereas in case of gram positive bacteria (*Bacillus subtilis*) with a 55.4 nm cell wall thickness had the highest resistance to CAP treatment [42]. The inactivation of bacteria is known occur via three different mechanisms which include: (i) Deoxyribonucleic Acid (DNA) direct chemical damage; (ii) Permeabilisation of cell membrane causing cell component leakage; (iii) Damage to intercellular proteins via nitrosative or oxidative species [43]. Cells go through a sequential set of morphological and physiological changes before being inactivated.

The experimental results of Kvam E et al., showed that the CAP treatment had damaged the outer membrane and cell wall of gram negative bacteria [44]. Recently, the cold plasma has acquired considered attention due to its efficacy in inactivation of surface contaminants. Joshi SG et al., had successfully designed Floating-Electrode Dielectric-Barrier Discharge (FE-DBD) for swift inactivation of bacterial contaminants in air [45]. Joshi SG et al., validated that the *E. coli* membrane lipid peroxidation can be done using FE-DBD [46].

The response of bacteria towards the CAP treatment depends on species type. It is observed that gram negative bacteria comparatively more sensitive than gram positive bacteria, which indicates that the impact of CAP treatment depends on cell wall thickness as well as cell membrane. The experimental results of Laroussi M et al., proves that CAP treatment had induced considerable damage to gram negative bacteria. Though, the outer membrane is absent in gram positive bacteria (*B. subtilis*) it is highly resistant due to its thick cell wall that ensures its rigidity. Further, even though cell structure of *B. subtilis* was not affected due to CAP treatment but cell viability reduced drastically [47].

The CAP treatment is used widely in disinfection of microbial biofilms. Biofilm is regarded as cell clusters of bacteria encapsulated via Extracellular Matrix (ECM) [48]. Biofilm cells have been shown to display greater drug resistance as compared to planktonic cells [49]. The existence of ECM in biofilms significantly impacts the efficacy of CAP treatment. The matrix consists of 3-dimensional biofilm structures wherein cell to cell communication is done via embedded cells. The matrix is different for various bacterial species. The matrix comprises of nucleic acids, polysaccharides, proteins and Extracellular Polymeric Substance (EPS) [50].

The EPS serves as good barrier for chemicals which include biocides, antibiotics and provide a shielding effect for photons, RONS, charged particles generated in CAP during treatment. Hence, longer treatment duration is essential for mediation of EPS structure and thereby imitating enzymatic degradation effect. Once the reliability of biofilm matrix is damaged then the biofilm cell in the interior is more vulnerable to inactivation [51]. The ECM is not the only factor that is accountable for variable killing time of biofilm cells but there are other factors like oxidative stress response to planktonic cells thereby enabling them to be highly resistant to antibiotics [52].

Previous studies also indicated the RONS is concentrated in microcolonies [53,54]. But low doses of oxidative stress found to have favoured the growth of biofilms (*S. aureus, E. coli*). *S. aureus* stimulates biofilm formation in an oxidant dependent manner also biofilm formation improves when it is exposed to hydrogen peroxide. Hence, the CAP treatment duration and dose must be carefully chosen to make sure eradication of only the biofilm cells without damaging the other cells.

Biofilm growth occurs mostly often in moist environment, hence it is imperative to decode the ambient air as well as interactions of CAP with liquid based surfaces. Numerous studies have proved that efficacy of CAP treatment is significantly higher in wet surfaces as compared to dry surfaces. Reactive species generated during CAP treatment penetrate via diffusion through liquid based medium [55,56].

In spite of various benefits of CAP treatments in liquid based medium, there are a few drawbacks such as production of numerous chemical species (nitrate, hydrogen) and generates acids [57]. The antibacterial effect of CAP on liquid based media depends on the reactive species generated during treatment [58]. Radicals also play a main role in fatty acid oxidation inside the bacterial cell thereby inactivating the microbe [59]. The inactivation time of microbes relies on the liquid volume [60]. Thus, it is seen that bactericidal effect of CAP treatment in liquid interfaces is due to the generation of RONS.

Virus Inactivation-Cold Plasma

Virus is one of the major microbes that have infected various cell-based living organisms that include- humans, plant, animals. Most of these virus strains have significantly impacted the medical, agricultural sectors both biologically as well as economically. Cold plasma implemented for virus disinfection is regarded as eco-friendly, efficient and novel technique for decontamination of virus. Most of these virus strains are not dangerous and few of them are much beneficial for their host organism [61,62]. Various chemical (alkalis, chlorine, alcohols, and bleach) and physical methods (filtration, temperature, UV irradiation, pressure) have been employed for killing viruses [62]. The disinfection method differs based the matrix type and virus type considered for inactivation. Plant virus (tobamoviruses) and waterborne viruses (enteric viruses) are most resistant of all viruses [63,64]. Strong disinfection methods are essential for disinfecting stable viruses and it imperative to ensure it maintains the quality of water with increasing in toxicity. Traditionally, chlorination has been implemented for decontamination of water and it's observed that it's inefficient in killing some virus strains along with increasing the toxicity of water resulting in a health hazard.

Recently, numerous inactivation techniques have been developed which includes-UV, ozone treatment, membrane filtration [64]. The intriguing composition of CAP which includes reactive species, molecules, radicals and charged species has resulted broad research on the implementation of CAP for decontamination of pathogens.

Enteric viruses: CAP treatments have mostly concentrated on enteric viruses such as adenovirus, hepatitis A virus and norovirus. These viruses have been the prominent cause of infectious diseases globally [65]. Experimental research work with human viruses poses significant health risk and such investigations need latest technology labs and equipment. Due to limited cultivation methodologies the impact of enteric viruses (norovirus) has been analysed only with limited research data. Owing to these limitations they are mostly replaced via surrogate viruses.

Animal viruses which include Tulane virus, Feline Calicivirus (FCV) and murine norovirus are implemented as surrogates for norovirus due to their similarity about genetics, similar sizes and morphologies. Due to their augmented safety and easier to reproduce these surrogate viruses are being implemented. Furthermore, few of viruses have also been found to infect bacteria known as bacteriophages, these can also be implemented as surrogates [66].

The surrogates and enteric viruses have been successfully treated in various mediums that include stainless steel, food surfaces, liquids, aqueous solutions [67-70]. It was distinctly observed that the efficacy of CAP treatment was significant in surrogate virus as compared to the enteric virus [69,70] which clearly suggests the experimental results of CAP treatment with surrogates cannot be directly into consideration for understanding the enteric virus [69,70].

The FCV inactivation in liquid (including bacteriophages) has been implemented by CAP treatment with duration of 15 s [71,72]. Though, its short period of treatment time this suggests that CAP treatment is most essential for inactivation of virus in liquid based medium.

The CAP treatment has been implemented on various types of food surfaces which include- meat, lettuce, blueberries wherein the viruses have been successfully inactivated without modifying the physical or chemical properties of food. Furthermore, dielectric barrier discharge based CAP treatment has been applied packaged food also [68,69,73,74]. As these are direct plasma treatment methods, the temperature at the point of treatment should kept within permissible limit to avoid thermal damage of food in certain conditions due to various generation CAP generation techniques. Indirect CAP treatment methods like plasma-activated liquids can also be used for microbial decontamination.

Respiratory viruses: Respiratory infections triggered by viruses are most important sources of upper and lower respiratory tract diseases. Among these the paramyxovirus and influenza virus are the major microbes. These viruses (influenza virus and paramyxovirus) are predominantly transmitted through air and by droplets of infected people.

One of the vital contents of CAP is ozone which is responsible for inactivation of viruses. The experimental results of Murray BK et al., proved that ozone triggers the peroxidation of proteins and lipids which in turn kills the virus [75]. Pulsed power based CAP treatment has been already implemented on Respiratory Syncytial Virus (RSV) and influenza virus [76]. In paediatric medicine this RSV is considered one of the most important virus as its transmission occurs via contaminated surfaces [77]. CAP treatment has also been implemented for efficient disinfection of various hospital devices (scalpels, dental instruments, clamps) [78]. As most of respiratory infections are airborne and since viruses causing them are very stable so it's imperative to sterilise the air to stop the virus transmissions which are airborne. The investigations done by Wu Y et al., and Xia T et al., showed successful eradication of MS2 bacteriophage using CAP treatment in duration of only 0.12 s and 0.25 s of contact time with CAP [79,80]. However, these CAP treatment techniques can at times be hazardous as ozone is produced in high concentrations. Thus, the CAP treatment employed for biomedical applications should be having ozone concentrations within the recommended safety limit [81].

Animal viruses: The most important viruses inactivation through CAP treatment are: Newcastle Virus (NV), Avian Influenza Virus (AIV), Porcine Reproductive and Respiratory Syndrome (PRRSv). These viruses impacted the food security and the economy. Some strains of NV can result in up to 100% mortality in bird species. Vaccines serve as the potent tool in offering better immunity via virus inactivation thereby reducing potential risk of disease [81]. Since, virus inactivation is preliminary step in vaccine preparation hence CAP treatment becomes quintessential to achieve the same.

Furthermore, there are few methods in which aqueous solutions activated by CAP treatment are employed successfully to disinfect tools and surfaces infected with poultry. Su X et al., proved that CAP activated aqueous solutions had completely inactivated viruses of avian embryos which attained 100% survival rate [82]. PRRSv is one the major microbes that has significantly impacted the pork industry. PRRSv is airborne virus which remains active even after traversing long distances [83].

Few of the most extensively employed methods for purifying air depends on either reducing virus contamination (different filters) or virus spread (UV irradiation). CAP treatment offers numerous advantages like curbing the spread of virus and killing them via charge driven filtration and RONS in CAP [84].

Plant viruses: Plant viruses are known to be predominantly transmitted via insects. These plant viruses are known to cause huge damage to crop globally resulting in economic downfall. The viral spread has been rapid due to various factors like closed irrigation system and untreated waste water [85]. In spite of this there are only few reports of CAP treatments inactivating these viral pathogens. which include water transmissible virus and potato virus [86,87]. Some of these economically significant plant viruses (Tobacco Mosaic Virus) (TMV) are found to be highly resistive and stable to various traditional inactivation methods. The experimental results of some studied showed DBD based CAP treatment for 10 minutes reduced the viral particles to subunit level and damaged the TMV Ribonucleic Acid (RNA) and thus successfully stopped spread of infection. Although, only few studies have been conducted for analysing the effect. Min SC et al., had successfully proved the inactivation of Tulane virus in roman lettuce using a DBD based CAP treatment [69]. These experimental results strongly suggests that plant viruses can be inactivated using CAP treatment without inducing any physiological damage to the plant species.

Fungi Inactivation-Cold Plasma

The CAP treatment is potent tool implemented in augmenting food safety and enhances shelf life. Fungal food spoilage has been a notable concern in the agriculture sector. Many of fungal infections once commenced is very tricky to disinfect as spores and fungal cells are known to demonstrate quite resistant structures. For inhibiting fungal spoilage of numerous fruits specifically citrus fruits. The traditional disinfection methods include wax coating, chemicals fungicides, [88].

To combat food security and satisfy the ever-growing consumer demands. Various CAP treatment technologies have been the scope of research in the agriculture sector.

Fungi are microbes which single celled or complex multicellular micro-organisms and nucleated. Fungi is further subdivided into different categories that include: (i) macroscopic filamentous fungi; (ii) multicellular filamentous moulds; (iii) single cell yeasts. Moulds comprise of fine threads known as hyphae. Hyphae branch out and form mycelium (network of threads).

Hayashi N et al., demonstrated the efficacy of atomic oxygen in killing *Penicillum digitatum* and *Aspergillus oryzae* [89]. Suhem K et al., had successfully implemented a RF-based plasma which inactivated *Aspergillus flavus* [90].

Avramidis G et al., applied atmospheric pressure DBD plasma treatment for disinfecting *Ascochyta pinodella* and *Fusarium culmorum* fungi [91]. After the CAP treatment it was observed that the cell membranes and cell wall structures were significantly affected which led to cytoplasm leakage [91].

Lee GJ et al., demonstrated that CAP treatment on Cordyceps bassaiana had significantly damaged its fungal spores causing wrinkling of surface, shrinkage, flattening and rupture and modified the fungal spores morphologically [92]. Experimental results of Dasan BG et al., showed that fungal spores of *Aspergillus parasiticus* were eradicated using CAP treatment and it also revealed the cell constituents scattered in clusters [93].

Extensive investigation on the impact of 1O2 (singlet oxygen) in killing fungi has been done by Hashizume H et al., [93-96]. Iseki S et al., employed atmospheric pressure plasma consisting of high density ground state atomic oxygen for inactivation of *Penicillium digitatum* fungal spores [97]. Eisenman HC and Casadevall A further proved that fungal spores consist of melanin (protective pigment) in the cell wall structure that shields it form external parameters such as UV radiation [98].

Thus, it can be concluded that CAP treatment causes leak of intracellular composition by damaging the cell wall structure of the fungi spores. It is imperative to note that magnitude of changes in fungi spores is directly proportional to its exposure to reactive plasma constituents (OH, H_2O_2, HNO_2, H, O, e-).

COLD ATMOSPHERIC PLASMA TREATMENT

CAP Treatment for Fungal Disinfection of Food

The CAP treatment has been extensively implemented for a wide variety of food stuffs that include- food grains, dried meat, nuts, fish, spices and herbs [99-106]. Whitehead indicated that plasma chemistry is specifically dependent on fine-tuning of various parameters which include plasma supply frequency, gas composition, input energy duration, pulse form, and modulation [107]. Also, CAP treatment is much preferred over other traditional decontamination techniques as it does not employ intense system [108-110]. Furthermore, CAP treatment eliminates pathogens in food stuff without causing any thermal damage to food products [111].

CAP Treatment in Wound Healing

The CAP treatment has played a pioneering role in wound healing. Preliminary investigations and experimental studies prove that CAP

are very efficient in enhancing healing of chronic wounds in both humans and animals without causing any considerable damage to healthy tissues [112-116]. These experimental results also showed that CAP treatments reduced the bacterial load substantially [117]. The investigations of Lou BS et al., established that CAP has the capability to disinfect microbes by damaging their DNA and via cell wall destruction thereby reducing the microbial load [117]. In addition to microbial disinfection the CAP treatments were also found to be instrumental in alteration of inflammation of chronic wound which transformed prevented the stagnation of wound [117]. Wound healing predominantly concerned with cell migration and proliferation as well as angiogenesis. Mainly, fibroblasts and keratinocytes are the cell types which enables wound healing, amongst which keratinocytes is played a key role in the main healing processes whereas the fibroblast cells played a guiding role [118]. Furthermore, the CAP treatments improved numerous growth aspects (neovascularisation/angiogenesis) along with reactive plasma species interaction (atomic oxygen, OH, NO) [118-121]. The CAP generates RONS that are capable for healing wounds and may accelerate the signalling paths to normalise tissue healing in the skin [122]. It is important to note that certain biological mechanisms such as cell proliferation and migration and tissue repair have been found to be accelerated by impact of RONS [123]. Ngo MHT et al., found that fibroblast growth was responsible for RONS induced endothelial cell proliferation [124].

The CAP due its distinctive characteristics and constituents have been widely employed in numerous biomedical applications such as wound healing, normalise drug resistant bacteria, and root canal treatment [125,126]. However, a numerous reports claimed that UV radiation in plasma is low and does not play a significant role in anti microorganism process except that from microwave driven discharge [127-130]. Furthermore, it is important to note that the plasma dose, gap between plasma source and specimen, duration of treatment is essential to optimise the efficacy of CAP treatment [131].

CAP Treatment in Dentistry

One of the most important advantages of CAP treatment is its ability to sterilise and treat irregular surfaces. CAP treatment in dentistry involves the reactive species in plasma interacting with internal dental cavity. Sladek REJ et al., demonstrated that plasma needles effectively inactivated *Escherichia coli* [132]. The results of Goree J et al., proved that CAP treatment effectively disinfected *Streptococcus mutans* [133]. Sladek REJ et al., examined the plasma interactions with dental tissue implemented via plasma needle [132]. Since, CAP treatment operates at room temperature it does not cause bulk destruction of the tissue. Furthermore, the sterilisation and cleaning of infected tissue in dental cavity can be implemented via laser or mechanical technique. In both these techniques there can be damage of healthy tissue as well as heating issue. To overcome these challenges the plasma needle is employed as efficient source containing reactive species to accomplish the microbial disinfection without harming the healthy tissue. The reactive species in gas phase produced by the plasma needle can interact on tooth surface and can dissolve into a liquid. Plasma needle generates bactericidal agents in treatment vicinity and penetrates fissure spaces and internal part of the dental cavity [134]. Yang B et al., designed plasma brush using argon as working gas. This plasma brush was found be highly efficient in decontamination and inactivating microbes such as *Streptococcus mutans* and *Lactobacillus acidophilus* [135]. Their experimental results suggested 100% bacterial disinfection within treatment time of 15 seconds for *Streptococcus mutans* and within five minutes for *Lactobacillus acidophilus*.

Thus, it can be summarised that CAP treatment is novel technology capable of microbial disinfection which can be implemented in narrow channels as well as irregular structures.

Adhesive restoration: Dong X et al., examined the effects of CAP treated dentin surfaces and their interaction with 2-Hydroxyethyl Methacrylate (HEMA), adhesive monomer [136]. Their experimental results clearly showed that argon based CAP treatment was very effective in enhancing adhesive monomer penetration and subsequently enhanced the dentin/adhesive interface bonding. Ritts AC et al., implemented CAP based brush for composite restoration [137]. Their results demonstrated that CAP treatment enhanced the surface characteristics of dentin which subsequently improved the bonding between adhesive restoration and dentin. Furthermore, CAP treated fiber-reinforced composite and resin were found to demonstrate better tensile shear bond as compared to traditional core [138].

Biofilms: Biofilms formed on the tooth surface results in periodontal diseases, dental cavity, oral mucositis and periodontal diseases. These biofilms also impact the dental implant resulting in conditions such as peri-implantitis and peri-mucositis. Furthermore, CAP treatment has the capacity penetrate and destroy biofilm matrix without damage to the oral tissue [139]. The study done by Koban I et al., found the CAP treatment has more efficacy in destroying the microbes (bacteria) present in dental biofilm in comparison to chemical antibacterial agents such as chlorhexidine [140]. Jiang C et al., implemented a plasma plume to decontaminate the root canal effectively at room temperature [141].

Tooth whitening: The CAP treatment has been widely implemented in tooth bleaching. Lee HW et al., demonstrated helium based CAP jet in combination with hydrogen peroxide solution (as catalyst) can be effectively used for tooth bleaching [142]. Their experimental results suggested that tooth bleaching effect generated by helium based CAP jet was due enhanced OH production and removal of tooth surface proteins. Nam SH et al. studied the effectiveness of tooth bleaching using CAP treatment (with 15% carbamide peroxide (CP; $CH_6N_2O_3$) including 5.4% Hydrogen Peroxide (HP), in comparison to other traditional light sources. Their results proved that CAP treatment was better and efficient in tooth bleaching without any resulting in any thermal damage as compared to conventional light sources (low concentration of hydrogen peroxide). Furthermore, direct current plasma jets (with hydrogen peroxide) have also been successfully implemented in tooth whitening [143]. The removal of intrinsic stains has presented big challenge during teeth bleaching [144]. Park JK et al., implemented a low frequency plasma source (used with hydrogen peroxide) for eliminating intrinsic stain [145]. The in-vitro investigations of Kim MS et al., showed that CAP treatment could be used for tooth bleaching [146]. They also found that the plasma treatment had not resulted in any damage to the tooth.

The CAP treatment has created an intriguing new era of dental care. The CAP treatment efficacy in various domains of dentistry (root canal disinfection, sterilisation, tooth whitening) has been encouraging for its wide implementation. As the oral disorders are polymicrobial nature, hence it's imperative to understand inactivation mechanism of CAP for each of these microbes responsible for dental plaque development. Further, there is research lacuna which needs to be investigated for understanding the CAP interaction with living tissues/cells.

CONCLUSION(S)

The CAP has been implemented as potent tool in wide spectrum of biomedical applications (food sterilisation, wound treatment, dentistry). It is seen that CAP is also very effective in inactivation and decontamination of microbes (bacteria, viruses, fungi). CAP treatment has also successfully inactivated food borne microbes responsible for food wastage. Furthermore, CAP has also been increasingly implemented for food processing techniques which enhance food quality (functional, sensory, texture properties). As CAP treatment is done at room temperature the thermal damage to the food or tissue is avoided. It also be noted CAP based medical devices have also

been tested and implemented for various biomedical applications. Thus, CAP has shown tremendous potential for its effectiveness in biomedical without modifying/damaging surface properties of tissues/cells.

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