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Effect of the Cold Atmospheric Plasma Technology for Treatment the Cancer Diseases in the Human: A literature Review

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ABSTRACT

CAP is a form of plasma with a temperature below 104°F at the application site. There are a variety of techniques for producing CAP, including Atmospheric Pressure Plasma Jet, Dielectric Barrier Discharge, and plasma needle and pencil. Multiple gases can produce CAP, including Helium, Heliox, Nitrogen, Argon, and air. Due to CAP's ability to deactivate organisms, cause cell separation, and kill cancer cells, researchers are interested in identifying dental and oncological applications for the compound. CAP is an ionized gas at 25 C°; it produces ROS and RNS due to several factors such as U.V., ray, heat, and power electric effects. Plasma is a matter at (fourth state) formed at low pressure or high temperature. Often, it is described as an ionized gas produced by the polyatomic fragmentation or the subtraction of electrons from monatomic gas shells. CAP has an antitumor effect. The current study aims to shed light on CAP technology, its definition, types, general applications, and their applications in treating human cancer. CAP was effective in treating cancer and eliminating tumor cells. CAP may have a place in the therapy of cancer. CAP used for cancer therapy has many advantages as a therapeutic method due to its effects of high selectivity, non-toxicity, combination potential, and adaptability. CAP eradicates cancer cells and uses this technique as a clinical therapeutic option that is effective and safe.

Keywords- cold atmospheric plasma, treatment, non-thermal plasma

I. INTRODUCTION

In 1879, William Crookes was the first person to discover plasma. Plasma, often known as the fourth state of matter, is responsible for 99 percent of the observable universe's composition. According to Gan L. et al.'s 2020 research, the other states of matter include fluids, solids, and gases.

Cold atmospheric plasma is an ionized gas that is formed around ambient temperature; it creates ROS and RNS and causes physical changes, such as U.V., ray, and electric effects (Gangemi, et al. 2022). Cold atmospheric plasma was discovered by Gangemi, et al. in 2022. The term "plasma" refers to the fourth state of matter, which may be created when the temperature is very high, or the pressure is very low in the field of physical science. According to certain definitions, it is an ionized gas that results from the polyatomic fragmentation or the electrons removal from the monatomic gas molecules (Adhikari B.R., et al. 2013).

Several investigations have shown that exposure to cold atmospheric plasma may induce apoptosis, necrosis, and autophagy in a wide variety of cell types, including neoplastic cells (Jin, et al. 2021). One of these experiments was conducted by Jin T. and his colleagues. This method can kill cancer cells by disrupting the more fragile redox equilibrium of tumor cells. However, it causes death of the immunogenic cell, provokes genetics, decreases angiogenesis, and epigenetic mutations (Kannan, et al. 2020).

The activation of solutions via the use of gas plasma technology is a novel approach to the treatment of hematological cancers and other types of tumors that are difficult to access. According to the research of Attri P. et al. 2021, the cold atmospheric plasma has an influence on hematological cancers. According to Dai, et al. 2023, plasma is a gas that is only partly ionized and contains

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uncharged particles, electrons, and ions. Thermal plasma and nonthermal plasma, often known as cold atmospheric plasma, are the two forms of plasma. Electrons and heavier particles, such as neutrals and ions, both exist at the same temperature in thermal plasma. According to Hoffmann, et al. (2013), CAP is considered nonthermal because its electrons are at higher temperatures.

CAP is a particular kind of plasma with a temperature lower than 104 degrees Fahrenheit at the location where it is applied (Tabares FL, et al. 2021). Several kinds of CAP are some ways that CAP may be manufactured (Bernhardt T., et al. 2019). Helium, argon, nitrogen, air, and heliox (a mixture of helium and oxygen) are some of the gases that may be used to create CAP (Kupke LS, et al. 2021). Other gases that can be employed include helium, argon, and nitrogen. CAP in cancer therapy is interesting by scientists (Boeckmann L. et al. 2020) due to the capability of CAP to inactivate bacteria, cell detachment forming, and cancer cell death.

The current study aims to focus light on cold atmospheric plasma technology, its definition, types, general uses, and, in the end, their uses in the treatment of cancer of the human body.

II. THE THEORETICAL ASPECT

Definition:

CAP is used plasma to form RONS to kill cancer cells (**Murillo et al. 2023).**

III. COLD ATMOSPHERIC PLASMA TYPES

1- Dielectric barrier discharge (DBD):

It is the discharge of electrical current that occurs between two electrodes that are isolated from one another by a dielectric barrier. Ernst Werner von Siemens was the one who first observed the phenomenon in 1857 (Matsuno, et al. 1998) (Kogelschatz, et al. 1999). At the time, it was referred to as a silent discharge (inaudible discharge), but it is also known as an ozone generation discharge and a partial discharge.

High voltage, with frequencies ranging from low R.F. to high microwave, is the current often used in the process. On the other hand, different techniques were developed to expand the range all the way down to the D.C. Covering one of the electrodes with a high-resistance coating was one approach used. The resistive barrier discharge is the name given to this phenomenon. These devices are able to be driven by a direct current voltage that ranges from 580 V to 740 V thanks to a different method that involves a semiconductor layer made of gallium arsenide replacing the dielectric layer (Jidenko, et al. 2009; Ebert, et al. 2007).

2- The Plasma jet:

Ignition occurring within a dielectric tube with a predetermined electrode arrangement, discharge propagation down that tube and subsequently in free space, and contact with surfaces are the characteristics that define plasma jets. Experimentation and simulation have been used to investigate the physics of plasma jets and how they interact with surfaces (Viegas et al. 2022).

The nonthermal atmospheric pressure plasma jet (APPJ), known as a cold atmospheric plasma jet (CAPJ), is a form of atmospheric pressure plasma jet (APPJ) that creates reactive species, such as ROS and RNS, with a gas temperature that is near to or exactly at room temperature. CAPJs have been put to use in a variety of biological applications, including the treatment of cancer and the healing of wounds. They are powered by a high voltage pulse that has a frequency of 88 kHz, amplitude of 14 kV, and a pulse width of around 1–1.5 picoseconds. A sinusoidal or positively pulsed voltage serves as the impetus for the creation of the plasma jet, and the excitation type ultimately decides the parameters of the CAPJ. Ignition occurs within a dielectric tube with a certain electrode configuration. The plasma jet is defined by discharge propagation along that tube and subsequently in free space and contact with surfaces. A review paper (Corbella, et al. 2023) and another review article (Schweigert, et al. 2023) have been written to provide the current state-of-the-art in creating CAPJs.

3- The plasma needle:

CAP needle is a form of plasma with a temperature at the point of application lower than 104 degrees Fahrenheit. This plasma is nonthermal because the electrons have a high temperature at (25) C^0. It has received great attention from researchers as a potential treatment in cancer and dentistry because it is an effective instrument for contemporary Medicine. The plasma needle has a diameter of 0.3 millimeters and is made out of a sharpened metal strand housed inside a tube made of perspex. The non-destructive atmospheric plasma could treat the fine surface of the biological components. The plasma needle, DBD, plasma pencil, and APPJ are types of CAP. CAP can be used in dentistry for making specific processes such as cavity preparation and restoration for the material's lifespan. CAP has physical effects on melanoma. CAP needle use in cancer therapy, tooth medicine, and stem cells. CAP inhibits the osteo-differentiation, cell migration and adhesiveness loss. Wang et al.'s research from 2020, the plasma needle used for the therapy of live tissues using plasma.

The cold atmospheric plasma needle has a variety of applications in the field of biomedicine. In dentistry, it has been utilized for cavity preparation and repair with enhanced lifespan. It is a non-destructive atmospheric plasma source for fine surface treatment of (bio) materials. Additionally, it has been shown to have a powerful anti-melanoma impact by the use of CAP therapy (Hoffmann et al. 2013) (Bran et al. 2020).

4- The plasma pencil:

In applications that involve indirect usage of plasma, a specific kind of plasma jet known as a CAP pencil may be used. It is a tiny portable device around the length and diameter of a big pen and is made

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up of a dielectric tube into which two disk-shaped electrodes of about the same diameter as the tube and which are separated by a small gap are placed. The length of the device is about the same as a large pen. When nanosecond-wide high voltage pulses at a kHz repetition rate are placed between the two electrodes and a gas combination (such as helium and oxygen) is flowed through the holes in the electrodes, the plasma pencil is ignited (Hoffmann et al. 2013). These conditions are necessary for the plasma pencil to function properly.

A plasma plume with lengths of up to 12 centimeters may be propelled through the aperture of the outer electrode and into the surrounding room air when plasma is ignited in the space between the electrodes. The chilly plasma plume released by the plasma pencil can eradicate germs without causing any damage to the surrounding skin tissue. In biomedicine, the plasma pencil has found applications in various fields, including wound healing, the elimination of oral germs, and the controlled surface modification of heat-sensitive materials. CAP could be used to treat many pathogenic bacteria, such as *E. coli*, and *P. gingivalis*. The plasma pencil is a mobile tool with a lightweight handheld (Jana et al. (1999).

Formation of the effect of a "shower" is done by the multiple plumes. The power generator can form big number of "Plasma Pencils," and stay stable at (25) C^{o} for several hours to provide the gas (Laroussi, and Lu, 2005). Laroussi and Lu. Reported that the power generator can service several "Plasma Pencils".

A cold plasma plume formed by a CAP pencil can also eliminate bacterial pathogens without any side effects on the normal tissue. It is used in many applications, such as wound healing and oral sterilization. CAP pencil is a mobile gadget that made up of a lightweight. Based on the results of Laroussi et al. (2006), produce an effect similar to a "shower" with several plumes, and it is organized in a series to treat bigger territories.

IV. COLD-PLASMA USES FOR MEDICINE

The synthesis of reactive oxygen species (ROS) may be achieved by CAP, making it a valuable tool in biomedicine. Previous studies have shown that CAP has anti-inflammatory, antiviral, and antibacterial characteristics, making it a viable therapeutic option for diverse medical conditions. Historically, the use of CAP was employed to eradicate microorganisms present in food and water, as well as to disinfect various surfaces. According to Lis et al. (2018), (Ercan et al., 2018, to be precise), Based on the results of several research studies, it has been shown that CAP demonstrates efficacy in eliminating a wide range of hazardous microorganisms. In addition to bacteria and fungi, the sample's composition also included antibiotic-resistant viruses such as SARS-CoV-2, as Chen et al. (2020) showed. Borges et al. (2018) have shown that using CAP has demonstrated efficacy in managing oral infections attributed to bacterial pathogens, including Candida albicans and Staphylococcus aureus. This is only one of the several capabilities that CAP has. The Civil Air Patrol (CAP) assumes responsibility for diverse services, as shown by the instance mentioned above.

In addition to possessing antibacterial properties, cationic antimicrobial peptides (CAP) have had a notable impact in expediting the wound healing process, as evidenced by studies conducted by Tan et al. (2021) and Amini et al. (2020). The role of CAP in infection elimination is accompanied by its ability to enhance cutaneous microcirculation (Borchardt et al., 2017). Additionally, CAP has been found to regulate blood coagulation (Nomura et al., 2017), stimulate the immune system, and promote the migration of fibroblasts and keratinocytes to the targeted area (Haertel et al., 2014). Furthermore, previous research has shown that CAP has the potential to enhance the proliferation of osteoblasts and provide improved adhesion, hence promoting the process of osteointegration in dental implants (Lee et al., 2017).

Researchers have also examined the use of CAP in Medicine. It has been shown that therapy with CAP may stimulate the regeneration of the nasal mucosa (Won et al. 2018), in addition to chondrogenesis and endochondral ossification (Eisenhauer et al. 2016). CAP can regenerate many types of neural cells. This is most likely owing to CAP's capacity to improve the stem cell characteristics of the neural stem cells (Xiong et al. 2019; Tan et al. 2020); these findings were published in two separate studies. According to Motaln et al. 2021, there are a variety of different processes by which direct CAP causes cancer cell death.

V. COLD-PLASMA USES FOR CANCER THERAPY

On the other hand, as was said previously, it is difficult to provide a specific mechanism of how CAP-based medicines cause the death of cancer cells. RONS are not focused therapy; each reactive species, ion, or charged particle may impact multiple cell signaling (Kumari et al. 2018). This is the reason why RONS are ineffective. In addition, since RONS are not targeted treatments, it is impossible to identify a particular mechanism of how cancer cells die when treated with CAP-based therapies. According to Khlyustova et al. 2019, the concentration of RONS produced by CAP is based on a number of different factors, including the kind of CAP device that was used, the treatment duration, the cell surface, the well plate, the volume of liquid, and the biochemical composition of the sample. Furthermore, the direct implementation of CAP jets used in biomedical applications might make it difficult to conduct

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fundamental molecular biology research. Consequently, scientists are frequently required to use PCLs to look into the signaling that are affected by CAP (Tornin et al. 2021).

Only the effects of RONS are taken into account as a result of this, and as a consequence of this, the findings cannot be directly compared to those of tests that employed direct CAP therapy. This is because the amount and form of RONS will be different; in addition, other elements, such as electromagnetic rays and the components of plasma that are still present, may also affect cellular responses. The use of CAP as a treatment for cancer is associated with a variety of potential advantages, some of which include the following:

1- Non-toxic:

The direct CAP treatment is safe to use since it does not generate potentially harmful byproducts or bring on any systemic adverse effects. In contrast, chemotherapeutic medicines and other anticancer treatments may produce a wide range of adverse effects, such as nausea, vomiting, loss of hair, and suppression of the immune system. the direct CAP does not result in the production of any potentially hazardous byproducts.

2- The ability to destroy cancer cells:

While sparing the surrounding normal cells selectively, CAP can eliminate cancer cells in a targeted manner. RONS are known to trigger cancer cell death by specifically destroying proteins, DNA, and other large molecules. CAP is responsible for creating RONS, which are accountable for this production. On the other hand, the vast majority of anticancer drugs are non-selective, which means that they kill both tumor cells and non-cancer cells together with the tumor cells they target. This causes the patients to experience negative side effects that are a consequence.

3- Adaptable:

It has a chance to be an effective treatment for solid tumors that are placed locally, and this potential stems from the fact that CAP can be directly given to the region where the tumor is. In addition, CAP may be given in a number of different methods, including administrated locally or IV, depending on the specific therapeutic setting in which it is being used. This is because CAP is quite versatile. CAP can treat a wide range of cancer stages and types due to its versatility, which makes it a very attractive option.

4- Combinatorial:

CAP is administered as a cancer therapy to improve the efficacy of the treatment and also to sidestep the harmful consequences of the drug non-response. The cancer cells will respond to the therapy resulting from CAP's ability to reverse the mechanisms that make the tumor cells change to cells resistant to the treatments. Murillo et al. 2023 found that CAP could stimulate the immune reaction to recognize the tumor cells, increasing the effectiveness of CAP's immunotherapies.

VI. PLASMA DEVICES IN CANCER THERAPY

The efficacy of CAP in cancer therapy depends on ROS capacity generation, safety, and the cell response Brandenburg et al. (2017). There are three primary categories of plasma sources: DBD plasmas, which are also known as "direct" plasma sources because they produce a discharge using the human body as an electrode; plasma needles and plasma jets, which are known as "indirect" plasma sources because they produce a discharge using two electrodes; and hybrid plasma sources, which combine the two types of plasma sources. According to several papers (Yan et al. 2017), plasma jets seem to be used more often than DBD plasmas. The utilization of these plasma-producing devices depends on the investigation's goal. The primary benefit of DBD plasmas is that they do not need for a specific flow of gas, which is necessary for plasma jets. Plasma jets typically involve the excitation of a noble gas using high-frequency electrodes. The DBD electrode has to be somewhat near the target in most applications, and its diameter may range anywhere from a few millimeters to several centimeters. In contrast to DBDs, plasma jets use three common gases, helium, argon, and nitrogen, to produce ROS (Joh et al. 2013). These gases determine the efficiency and pattern of ROS generation.

Other important factors to consider while operating plasma jets are the velocity of gas flow, the voltage being applied, and the distance separating the nozzle from the target. For instance, according to Schmidt-Bleker et al. (2016), increasing the distance between a target and a jet nozzle lowers the concentration as well as the diversity of most reactive species that reach that target, while other reactive species, such as ozone, are often shown to rise. Additionally, feed gas flux alterations are followed by reactive species composition alterations, particularly when the flow shifts from laminar to turbulent (Iseni et al. 2014).

The length of the exposure is still another essential component. According to research conducted in the field of microbiology, it is common knowledge that the growth inhibition of the bacteria increases as the amount of time that plasma is treated is increased. Similarly, the length of time the plasma is treated determines the magnitude of the biological reactions, such as apoptosis (Bekeschus et al. 2017). In addition, the length of time exposed to a substance may influence the release of cell-signaling molecules, such as cytokines and growth factors. The working settings of the plasma devices have an effect on the kind and the quantity of reactive species products, particularly in cancer cells. According to Arndt et al. 2015, controlling these circumstances results in an increase in plasma's ability to suppress the growth of cancer cells.

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VII. CONCLUSION

As a result of its antitumor effect on cancer cells, CAP has a promising future in the field of oncology. Researchers found that CAP has promising outcomes in cancer therapy, namely in destroying tumor cells. It is clear from the encouraging findings that were acquired from the reports of the effects of CAP on cancer. Compared to other therapeutic approaches, the usage of CAP as a cancer therapy has several benefits that set it apart from the competition. These benefits include its non-toxicity and high selectivity. Further study is required to completely understand the processes by which CAP eliminates cancer cells, which will eventually contribute to the development of a clinical treatment option that makes use of this safe and sufficient technology.

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