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Review Article

A Review of Plasma's Effects in The Treatment of Cancer

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Abstract: A recent area of plasma therapy is plasma oncology, or cool atmosphere radiation (CAP), which was the usage to prevent disease. This review's findings from multiple research demonstrate that CAP is efficient against cancer In either living tissue in addition to in cell culture lymphocytes. It has been demonstrated that CAP is more effective than conventional treatments at slowing the growth of cancer cells and, at greater doses, in inducing cell death. Furthermore, preliminary findings suggest that CAP may be selective for cancer cells since it is more efficient against tumour cells than against healthy non-cancerous cells. The prospect that CAP might be an intriguing new treatment method in this sector has been fueled by the recent advancements in the cancer therapy. Non-thermal plasma is a brand-new method of treating cancer. There are both direct and indirect plasma therapies available, and direct plasma therapy clinical studies are now being conducted. Chemotherapy (also known as plasma-activated medium) and immunotherapy are examples of indirect therapies. Recent research indicates that integrated plasma therapies may be a highly successful method of cancer treatment. Recent developments in atmospheric plasmas have produced cold plasmas with ions that are nearly at room temperature. This paper discusses current developments in cold plasma physics knowledge as well as using cold atmospheric plasma (CAP) for the therapy for tumours. Recently, several innovative plasma diagnostic methods have been created in an effort to comprehend the physics of CAP.

Keywords: Plasma-Activated Medium (PAM), Cold Atmospheric Plasma, Cancer Therapy, Plasma Selectivity, Plasma Medicine, Plasma Oncology, And Plasma Cancer Treatment;

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1. INTRODUCTION

The review highlights the potential of plasma cell death and restrict tumour growth, making it an exciting strategy for the therapy of cancer. To fully understand the mechanisms of plasma-induced cancer cell, nevertheless, more research is required. death and optimize its clinical application. Plasma therapy was developed as a result of research study of the application of low-temperature atmospheric plasmas in bioengineering for reactive nitrogen species (RNS), ultraviolet (UV), and other chemicals. a branch of science that is still relatively new [1-3]. Both ROS and RNS have been shown to cause oxidative stress and activate several cell signaling pathways. The method through which CAP interacts with live tissue is still unknown. The manner CAP is produced can have a range of distinct consequences on plasma. In actuality, CAP is a reactive nitrogen species, charge particles, ultraviolet, etc. The diversity of outcomes listed above are caused by this variety of species. Low temperature plasmas can be used directly on living tissues to kill pathogens, stop bleeding without harming healthy tissue, sanitise wounds and speed up wound healing, and even trigger apoptosis in some cancer cells in vitro. These research endeavours serve as the cornerstone of a novel approach to healthcare and form the core of the field of study known as plasma medicine [4-8]. Experiments on eukaryotic cells showed that under some circumstances, low temperature plasmas appear to harm Very little in living animal and plant tissues9,10. For example, skin cell divisions are being shown to be capable of surviving in hemoglobin under circumstances that may be lethal to microbial cells. The failure of current medical therapy to appropriately treat chronic wounds like diabetic ulcers results in thousands of organ losses every year in the country of America only. The main argument for complementary therapies like BTPs is that they are unsuccessful. Recent developments in the use of plasma suggest that lighting, substance, and dose-related react substances can all have an impact on the structural makeup of cells with cancer. Researchers in the disciplines of laser therapy for medicine, in general, have looked into how serum interacts with other substances. with various substances in order to facilitate further development and, more importantly, to fine-tune the parameters of the plasma devices as an alternative to current cancer therapy without the potential adverse reactions related to current chemotherapy power structures. It appears that cold atmospheric plasma (CAP) could be a novel type of cancer treatment. More generally, CAP has undergone testing for a variety of purposes, involving healing injuries, disinfection, dentistry, and cancer therapy [11-14]. Both in vitro and in vivo, CAP treatment has been proven to have potent fatal effects against tumour cells. Additionally, and perhaps more importantly, The same CAP therapy has also been demonstrated to have proved less harmful to normal equivalent cells15. This is really a multiple scales process that starts with a first wave at the time scale of milliseconds, progresses through the time scale of minutes, which is related to the brain, and concludes with the reactivation of several pathways in cells at the time range of several days or hours. A ROS is a positive ion that destroys cells. In addition, ROS are widely recognised for their capacity to irreversibly damage crucial proteins and nucleic acid components, such as the two substances.

1.1 Plasma Diagnostics

Visual discharge spectroscopy to electrical measurements of the discharge parameters, and imaging device (ICCD) lenses are a few of the diagnostic methods created to look at CAP 16-21. Among the active spectroscopic methods used were troscopy, laser absorbance spectral analysis, and small-scale Rayleigh, Thomson, and Raman scattering of laser energy. In recent years, novel methods that allow for temporally-resolved studies of radio conduct and weight, electrical currents in plasma jets, electric potential, and charge carried in the front of ionisation were presented. These methods involve streamer control using an external electric potential and microwave heat dispersion (RMS) on the plasma stream.

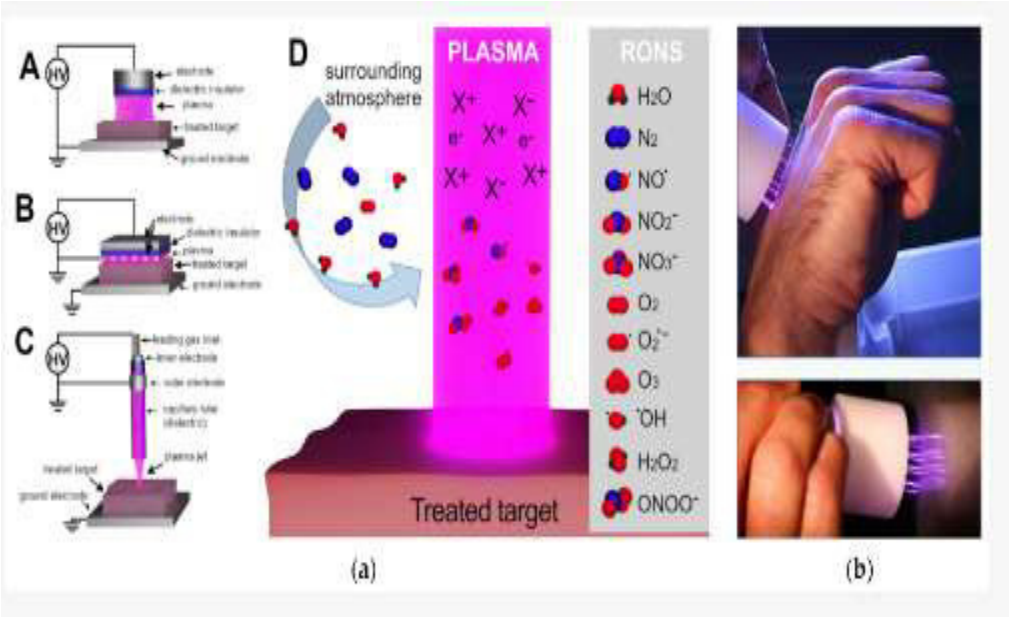

Fig 1. Images of a plasma multi-jet source intended for skin care [22,23]

1.2 Plasma interaction with liquids

Plasma interaction with liquids results in chemical reactions that can produce a variety of species in an aqueous solution is one of the crucial features of plasma application in bioengineering and medicine. Amidation and ring-opening of five-membered rings in histidine and proline, as well as hydroxylation and nitration of aromatic rings in tyrosine, phenylalanine, and tryptophan, as well as cysteine's thiol groups and methionine's sulphur oxidation, are among the chemical modifications of 14 amino acids that can be seen after CAP treatment[24,25]. The interaction of the CAP with the cell culture media may result in a considerable pH decrease and eventual cell death. In particular, increased doses of the CAP-containing cell culture media may cause the pH to decrease over time, from 8.5 to 5.5[26,27].

1.3 Molecular mechanisms of the cold atmospheric plasma

The main mechanism of CAP anti-cancer therapy as it is currently understood involves the generation of ROS and RNS. In'redox' or oxidation-reduction biology, both ROS and RNS play a crucial role. In biological systems, ROS and RNS both have significant functions. An anti-oxidant system reduces an overabundance of ROS. Reactive oxygen species are produced either directly or indirectly by the vast majority of the agents used to directly kill cancer cells (ionising radiation, the bulk of chemotherapeutic drugs, and some targeted therapies)[28,29]. These ROS inhibit important cell cycle events. It has been demonstrated that modest levels of ROS have a positive impact by promoting pathways for cell survival and proliferation. On the other hand, oxidative stress, which can result in cell death, is caused when the level of ROS rises excessively[30]. A cell uses antioxidants to combat such oxidative stress and stop ROS from building up to dangerous levels. It is well recognised that a considerable rise in intracellular ROS causes DNA damage and cell death in the targeted tissues.

1.4 The current developments in "plasma oncology"

The researchers demonstrated that the primary causes of these effects were the induction of apoptosis and, to a lesser extent, cell cycle arrest. They claimed that fluorescence probes and ROS pre-treatment were the main mediators of the therapeutic effects of ROS. In a separate strategy[37], the effects of CAP in pancreatic cancer cells were used as a tumour chorio-allantoic model. Several aspects of in vivo tumour growth, such as angiogenesis, are addressed in this organoid model in which tumour cells are implanted into eggs[31]. Recently, a plasma therapy developed that would be especially fascinating to oncologists. It has been established that CAP therapy appears to work better in cancer cells than in non-neoplastic cells, laying the groundwork for a targeted approach[32,33]. It has been demonstrated that plasma therapy causes growth arrest in melanoma cells after a brief exposure and considerable cell death after a longer exposure, with the effects being significantly more evident in the cancer cells and Keidar et al. examined various tumour types in a sophisticated analysis and contrasted their responses with those of normal non-neoplastic cells[34]. Once more, plasma effects were significantly more prominent in cancer cells [38].

1.5 Direct Treatments

The easiest treatments involve direct plasma. For medicinal purposes, such as the treatment of cancer, many different plasma sources have been established [39-40]. Advanced head and neck cancer ulcerations and patients with the disease's last stages were treated by Metelmann et al. with kINPen MED plasma [44,45] . Pain and odour were both lessened by plasma therapy. Few myeloid cells were found in the tumour tissue of patients who frequently received plasma therapy, but many myeloid cells were discovered in tissue samples from patients who did not receive plasma therapy. Using a Canady Helios Cold Plasma Scalpel, Canady et al. successfully treated liver cancer by removing malignant tissue without compromising the blood flow to healthy tissue.

1.6 *Indirect Treatment*:

Non-thermal plasma therapy produces ICD and activates macrophages, according to a number of recent research [46-49]. It was demonstrated that non-thermal plasma therapy increased cell death by enhancing extracellular ATP release and ICD-mediated macrophage activation. Reactive oxygen species (ROS) produced by plasma are important ICD effectors. The externalisation of CRT is inhibited by the ROS scavenger N-acetyl cysteine and is induced by non-thermal plasma. These findings imply that plasma-induced CRT production is mediated by intracellular ROS. Plasma-activated macrophages release tumour necrosis factor-alpha, which causes tumour cell death[50].

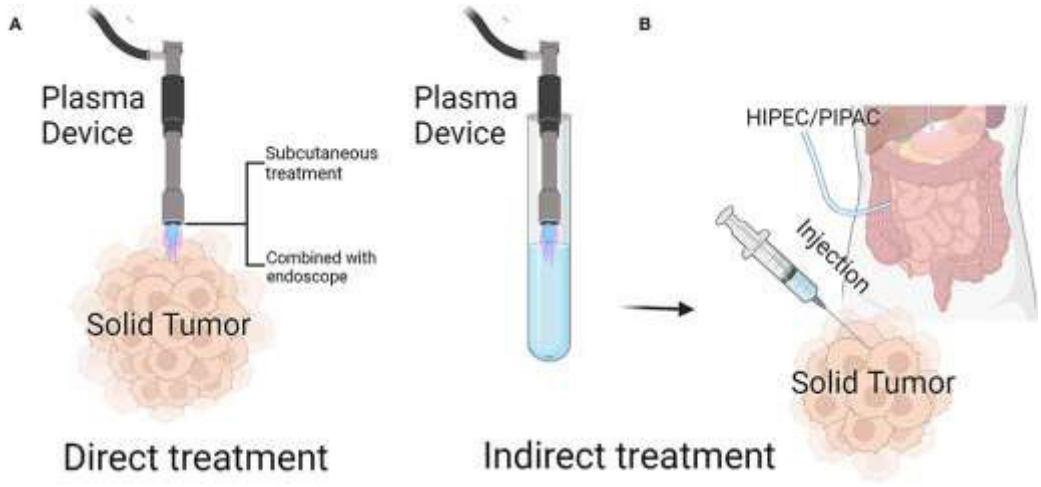

Fig 2. Treatment of solid tumors by cold atmospheric plasma (CAP)[66]

1.7 Indirect Treatment: PAM

PAM has been suggested as a kind of chemotherapy for cancer. PAM inhibits the growth of several types of cancer cells, as shown by numerous in vitro investigations. PAM typically causes intracellular ROS generation and subsequently cancer cell death [51-54]. Depending on the cell type, PAM promotes apoptosis in cancer cells by a different mechanism. In disease model mouse studies investigating peritoneal metastasis, intraperitoneal injection of PAM/plasma-activated Ringer's lactate (PAL) prevented the metastasis of ovarian, gastric, and pancreatic cancer tumours [55-57].

1.8 Direct plasma

Living tissue is directly involved in the active discharge plasma processes in direct plasmas because living tissue or organs are used as one of the electrodes. Living tissue may experience a modest amount of displacement current, conduction current, or both types of current. Direct plasma has emerged as a groundbreaking approach in the field of cancer treatment, offering exciting prospects for improved therapeutic outcomes. This innovative technique involves the direct application of ionized gas, known as plasma, to cancerous tumors. Direct plasma treatment harnesses the unique properties of plasma, such as its ability to generate reactive oxygen species (ROS) and release high-energy photons, to induce selective tumor cell destruction while minimizing harm to surrounding healthy tissues. One key advantage of direct plasma for cancer treatment is its ability to target and eradicate tumor cells through multiple mechanisms. The ROS generated by plasma can cause oxidative stress, leading to DNA damage and subsequent cell death. Additionally, the high-energy photons emitted by plasma can penetrate the tumor tissue and directly induce apoptosis, further inhibiting tumor growth. These dual mechanisms of action make direct plasma an attractive option for effectively treating various types of cancer. Moreover, direct plasma therapy offers several advantages over traditional cancer treatments. It is a non-invasive procedure that can be performed with precision, enabling targeted treatment of specific tumor locations. Additionally, direct plasma has shown promise in overcoming multidrug resistance, a significant challenge in cancer treatment. By utilizing plasma's unique properties, direct plasma therapy has the potential to enhance the effectiveness of chemotherapy drugs and improve treatment outcomes for patients. Direct plasma therapy represents a promising frontier in cancer treatment, leveraging the power of plasma to selectively destroy tumor cells while minimizing damage to healthy tissues. Its targeted approach, ability to induce apoptosis, and potential to overcome drug resistance make it an exciting avenue for advancing cancer therapeutics. Further research and clinical trials are crucial to fully explore the potential of direct plasma and optimize its application in clinical settings.

1.9 Indirect plasma

Indirect plasma has emerged as a promising approach for cancer treatment, offering potential benefits and advancements in the field. This innovative technique utilizes ionized gas, also known as plasma, to induce biological effects that can selectively target cancer cells while minimizing damage to healthy tissue. Unlike direct plasma treatments that involve the application of plasma directly to the tumor site, indirect plasma treatments utilize plasma-activated liquids or gases to deliver the therapeutic effects. One significant advantage of indirect plasma for cancer treatment is its ability to generate reactive oxygen and nitrogen species (RONS). These highly reactive molecules have been shown to induce cell death and disrupt cancer cell metabolism, effectively inhibiting tumor growth. Moreover, RONS can activate various signaling pathways that stimulate immune responses, enhancing the body's natural defense mechanisms against cancer cells. Indirect plasma also offers a non-invasive and versatile approach to cancer treatment. It can be applied through different delivery methods, such as spraying or injecting plasma-activated liquids or gases. This flexibility allows for targeted treatment of specific tumor sites or even systemic application to address metastatic cancer. Furthermore, indirect plasma therapy shows promise in overcoming drug resistance in cancer cells. Plasma-activated liquids can improve the effectiveness of chemotherapy drugs by increasing their uptake and enhancing their cytotoxic effects on cancer cells. This combination therapy approach has the potential to improve treatment outcomes and

reduce the risk of tumor recurrence. In conclusion, indirect plasma therapy represents a promising avenue for cancer treatment, harnessing the power of plasma to selectively target cancer cells, activate immune responses, and enhance the efficacy of traditional treatments. Continued research and development in this field hold the potential to revolutionize cancer therapy and provide new hope for patients worldwide.

1.10 Hybrid plasmas

Hybrid plasmas are created by using a grounded wire mesh electrode, which has a far lower electrical resistance than the skin and combines the direct plasma production method with the indirect plasma's current-free quality. Hybrid plasma therapy has emerged as a cutting-edge approach in the field of cancer treatment, combining the advantages of both direct and indirect plasma techniques. This innovative method involves the application of plasma-activated liquids or gases that are enriched with specific agents or nanoparticles to enhance their therapeutic effects. By integrating these additional elements, hybrid plasma therapy offers improved targeting and selectivity, as well as enhanced cytotoxicity against cancer cells. One of the key advantages of hybrid plasma therapy is its ability to combine the direct tumor-destructive properties of plasma with the targeted delivery of therapeutic agents. The plasma-activated liquids or gases can carry nanoparticles or drugs that are specifically designed to accumulate in tumor tissues. Once activated by the plasma, these agents can selectively release their cargo within the tumor microenvironment, leading to localized and intensified anticancer effects. Furthermore, hybrid plasma therapy holds promise for synergistic effects between plasma and therapeutic agents. Plasma-generated reactive species can enhance the efficacy of the delivered drugs or nanoparticles by promoting their uptake and improving their intracellular distribution within cancer cells. This combination approach has the potential to overcome drug resistance and improve treatment outcome Hybrid plasma therapy represents a promising frontier in cancer treatment, integrating the strengths of both direct and indirect plasma techniques. By combining plasma with targeted therapeutic agents or nanoparticles, this approach offers improved tumor targeting, enhanced cytotoxicity, and the potential for synergistic effects. Continued research and development in this field have the potential to revolutionize cancer therapy and improve patient outcomes.

1.11 Plasma Interaction with Cancer Cells

The use of CAP in the treatment of cancer is among its most promising medical uses. In order to ascertain the effectiveness of CAP in cancer therapy, the effect of cold plasma on several cancer cell lines was investigated. Lung, bladder, skin, head & neck, brain, and other cancer cell lines are among those taken into consideration[58]. Cold atmospheric plasma (CAP) has emerged as a novel and promising approach for cancer treatment. Unlike traditional plasma treatments that rely on high temperatures, CAP operates at near room temperature, making it safer and more suitable for medical applications. CAP is generated by ionizing gas in a controlled environment, creating a mixture of reactive species, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). One significant advantage of CAP in cancer treatment is its selective cytotoxicity towards cancer cells while sparing normal cells. CAP induces oxidative stress in cancer cells, leading to DNA damage and cell death. Normal cells, on the other hand, have more efficient antioxidant defense mechanisms, making them less susceptible to CAP-induced damage. Moreover, CAP has shown potential in promoting immunogenic cell death, which can trigger an immune response against cancer cells. This can enhance the body's natural defense mechanisms and potentially prevent tumor recurrence. Additionally, CAP has the ability to induce apoptosis and inhibit the proliferation of cancer cells through multiple pathways. It can disrupt cell signaling, inhibit angiogenesis, and modulate gene expression, contributing to its antitumor effect Cold atmospheric plasma represents a promising and safer approach for cancer treatment. Its selective cytotoxicity, ability to promote immunogenic cell death, and multiple pathways of action make it a potential game-changer in the field of oncology. Further research and clinical studies are needed to fully understand its mechanisms and optimize its application in cancer therapy.

1.12 Non-Equilibrium Low Temperature Plasmas

Non-thermal (or non-equilibrium) AP plasmas, also known as NTPs in this work, are widely used in low-temperature applications like material processing and biomedical ones due to their capacity to achieve increased gas phase chemistry at low gas temperatures. In recent years, a variety of plasma discharge sources that can produce stable and comparatively homogeneous plasmas at or near the AP have been produced and characterized. [59,60] DC-driven plasmas were produced using micro discharge structures and semiconductor manufacturing methods. By having cathode dimensions in the micrometer range, which enable an increase in pressure while retaining a relatively low sustaining voltage, micro discharges produce high-pressure non-thermal plasmas. The dielectric barrier discharge (DBD) is one of the most frequently used NTP generators [61]. DBDs use high voltages in the kHz frequency range to initiate the discharge and cover one or both of their two electrodes with dielectric materials. There have been applications of both cylinder and planar electrode with devices that resemble DBDs and with devices that have bare metal electrodes, radio frequency (RF) sources were also used to create NTPs [62]. Arcing is a concern when using bare metal electrodes, therefore one must manage both the electrodes' temperature (which is commonly controlled by cooling them with water) and the gas flow rate to reduce the likelihood of drawing arcs. The plasma pencil was put to use in biomedical applications to show its capacity for eliminating cancer cells, amyloid fibres, and different kinds of germs [63]. Because the plasma plume's cross-section is small, the therapy

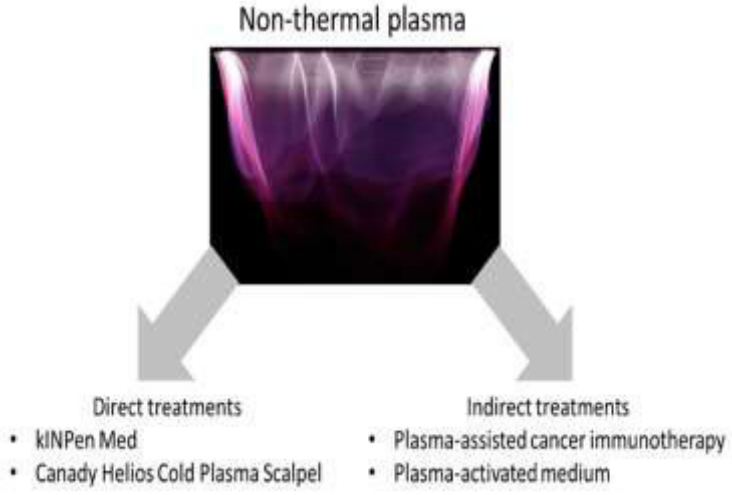

Fig 3. Two types of plasma-based cancer treatments. [67]

1.13 Biologically Tolerant Atmospheric Pressure Plasma Effects on Cancer Cells

The use of various machines that produce low temperature plasmas in a variety of biological applications is included in the field of plasma medicine. It is a superb treatment for cancer therapy due to the complex nature of the plasma properties and the interaction of the reactive species with biological cells. Since the heavy species like ions and neutrals stay within the biologically tolerant temperature range for treating eukaryotic cells[64], the NTP does not cause thermal damage, in contrast to laser and thermal therapy for cancer.

1.14 Cap Mechanism

Biologically tolerant atmospheric pressure plasma (APP) has gained significant attention as a potential treatment modality for cancer cells. Unlike conventional plasma therapies, which may cause damage to healthy tissues due to high temperatures or direct contact, APP operates at near room temperature and can be safely applied to biological systems. This makes it an attractive option for cancer treatment. One key advantage of biologically tolerant APP is its selective cytotoxicity towards cancer cells while preserving the viability of normal cells. APP induces the generation of reactive oxygen species (ROS) and reactive nitrogen species (RNS), leading to oxidative stress and DNA damage specifically in cancer cells. Normal cells possess robust antioxidant mechanisms that can effectively neutralize these reactive species, thus minimizing their detrimental effects. Furthermore, biologically tolerant APP has been shown to modulate cancer cell behavior by influencing various signaling pathways. It can inhibit cell proliferation, induce apoptosis, and disrupt tumor angiogenesis, thereby impeding the growth and metastasis of cancer cells. Another potential benefit of biologically tolerant APP is its immunomodulatory effects. It can stimulate the release of pro-inflammatory cytokines, activate immune cells, and enhance the body's immune response against cancer cells. This immunomodulatory effect can synergistically complement other cancer treatments and contribute to improved outcomes. Biologically tolerant atmospheric pressure plasma offers an exciting prospect for cancer treatment. Its selective cytotoxicity towards cancer cells, ability to modulate cell behavior, and immunomodulatory effects make it a promising avenue for further research and development. Continued studies are required to fully understand the mechanisms underlying its effects on cancer cells and optimize its application in clinical settings. ROS and RNS production is thought to be the cause of CAP action on live tissue. It has been hypothesised that the chemical, photodynamic, and radiation impacts are connected to the RON/RNS (or RONS) created by the plasma. In essence, this is a multi-scale process that begins with the initial burst at the time scale of nano and micro seconds (depending on the specific plasma device) to seconds, is followed by the time scale of minutes, which is related to RONS formation and transport across the cellular membrane, and finally triggers various cellular pathways at the time scale of hours and days. Due to their function in apoptosis, an internal process that results in cell death, ROS are referred to as "a positive force for life". At the same time, ROS are also well known "for their ability to irreversibly damage key proteins and nucleic acid molecules (e.g., DNA and RNA)." It is widely known how cells respond to an overabundance of ROS. It is known that the main enzyme that regulates H_2O_2 levels in both cancerous and healthy cells is catalase[65].

2. CONCLUSION

This review's from multiple studies demonstrate that CAP is efficient against cancer cells both in vitro and in vivo. Plasma therapy causes apoptosis in medium dosages and cell cycle arrest in low levels. Reactive species, especially reactive oxygen species (ROS), appear to be a mediator of these effects. The creation of new plasma devices for medical purposes, such as endoscopic devices, and combination techniques in the adjuvant cancer therapy, involving plasma mediated drug transport and drug activity, highlight the promise of this innovative approach. It was discovered that selectivity may be connected to the CAP effect on the cancer cells' cell cycle. It is also demonstrated that a

higher proportion of cancer cells are in the S phase, making them more vulnerable to the effects of CAP. the plasma pencil can serve as a prototype device to produce low temperature plasma for use in preventing the spread of various malignancies.

3. CONFLICT OF INTEREST

Conflict of interest declared none

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