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Review Article

A Review of New Method of Cold Plasma in Cancer Treatment

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Abstract: Cold atmospheric plasma (CAP) is a semi-ionizing gas with ions, electrons, and particles without charge such as atoms. CAP is produced by different methods such as atmospheric plasma jet (APPJ), pencil plasma and needle plasma. Today, the CAP along with other methods of cancer treatment used to in oncology. This study provides some information about the structure, different methods of production and the general mechanisms of cold atmospheric plasma. Furthermore, this study explores and interprets the results of studies done about the influence of cold atmospheric Plasma on cancer cells. Articles express investigated the relationship between cold atmospheric plasma and improved outcomes of cancer treatment. Cold atmospheric plasma through mechanisms such as activating protein P53, enabling inhibitor P21CDK, stop the cell cycle in phase G2 / M phase and S, stimulate apoptosis through ROS production and disable the mitochondria and so on, leading to tumor cell death. So it can be as a good therapy method is effective in destroying cancer cells. Case studies have shown that the use of cold atmospheric plasma in treatment of cancer patients, Not only will quickly eradicate tumors, but increases the median survival in patients. Moreover, the exact mechanism of cold atmospheric plasma action is still unknown that can be the subject of future research.

Keywords: Cold atmospheric plasma, CAP, cancer treatment, cancer cells.

INTRODUCTION

Cancer as a tumor or malignant neoplasm is included a range of different diseases in different parts of the body. Today, despite significant advances in medical science, Cancer remains one of the most important diseases of the present century and the second cause of death after cardiovascular diseases. This disease is delineating to the deformation of the abnormal cells and loss of cell differentiation. Now, more than 7 million people worldwide lose their lives due to cancer and it is predicted that attain the number of new cases to year 2020 from 10 million to 15 million [1, 2]. In 2012, about 1/14 million new cases of cancer in the world happened that this amount was cause of 6.14% of human deaths [3, 4].

Probable symptom this chronic disease include: Unusual masses, unusual discharge, loss of body weight without antiseptic cause and changes in bowel habits, etc [5]. Recently researchers have shown in their research that is accounted Tobacco by 22%, the highest rate in cancer, for 10% due to factors such as: Obesity, Life Without proper diet, decreased physical mobility and alcohol drinking and range 5-10% have been affected by genetic. Infection, exposure to ionizing radiation and environmental pollutants is as well as other factors are considered incurable disease [6 ,7].

Cancer treatment is often a combination of surgery, radiation therapy, chemotherapy, hormonal therapy and biological therapy. This treatment is used sake destroy cancer cells and to return health [8]. The signs diagnosis and follow-up are an important part of the treatment and according to the person who has cancer; experts or a combination of these treatments is used.

Recently a new method that is of interest to researchers in cancer treatment is cold atmospheric plasmas (CAP). This treatment method during inactivating bacteria, fungi and spores do not harm to healthy normal tissue and in combination with chemotherapy is effective. That in our country this method don't find its place among other of treatment methods, in this article we are going to search this kind of treatment.

HISTORY AND ADVANTAGES COLD PLASMA

In 1879 William Crookes discovered plasma. In his research found that 99% of the space made up of plasma. Plasma is a half-ionizing gas with ions, electrons and particles without charge such as atoms, molecules and radicals. In general, the plasma can be divided into 2 types: Thermal plasma and cold plasma or plasma non thermal. plasma is consisting of electrons and heavy particles (ions and neutrons) at the same

temperature. Non thermal plasma or cold plasma is contains electrons that are in higher temperature than the heavy particles. Cold plasma is applied in temperature of less than $F^{\circ} 104$ [9]. Recent advances in cold plasma are caused the production plasma containing ions in the temperature close to room temperature [10]. This type of plasma can be no electrical and thermal damage to the cell surface, absorption the organic material [11, 12]. Some researchers believe that ions play a crucial role in cell-plasma interaction through the establishment of intracellular biochemical processes [13]. On the other hand, some have suggested that neutral particles have the important and primary role in plasma-cell interactions [14]. Moreover, different effects of ion may be quite selective, some of them can be lethal effects (such as oxygen) and some therapeutic effect (such as nitrogen monoxide) [10, 15].

METHOD COLD PLASMA PRODUCTION

Various gases such as helium, argon, nitrogen, Heliox (mixture of oxygen and helium) and air and energy such as heat, electricity and light energy used for produce and maintain plasma [9]. Various methods exist for the production of cold atmospheric plasma as follows: Dielectric discharge (DBD), atmospheric plasma jet (APPJ), needle plasma and plasma pencil.

DIELECTRIC DISCHARGE (DBD)

Siemens in 1857 was the first to perform experiments on the DBD. A DBD application is include

sterilization of living tissue, inactivating bacteria, angiogenesis, surface treatment and etc. DBD consists of two planar metal electrodes that covered by a dielectric material and between them exist a ionized gas for produce a plasma. One of the electrodes is the high voltage electrode and other electrode is the underlying electrode. For manufacturing processes discharge required to produce plasma is needed high voltage. Generally, high voltage caused production KHz frequency range of the DBD and consumption rate of energy is between 100-10 w [16]. Number of DBD electrodes in various surveys is different, but all comments are almost identical; For example, some of electrodes are flat instead of cylindrical and sometimes only one of the electrodes is covered by a dielectric.

Recently Chirokov et-al used planar electrodes FE-DBD (floating-electrode DBD) [17]. FE-DBD is exactly the same as the original DBD contains two electrodes, one of electrodes is insulated high voltage and the second electrode is active. The difference between DBD and FE-DBD is in the second electrode that this is not underlying rather is active, this means that the second electrode can be of a sample of human skin or any organ of the body. The FE-DBD used in endothelial cells, skin melanoma and hematologic malignancies. FE-DBD also is used in the sterilization of living tissue and disables bacteria *Stratus Frikus* [18-22]. Currently plasma jets that used of DBD system also are produce [23-25].

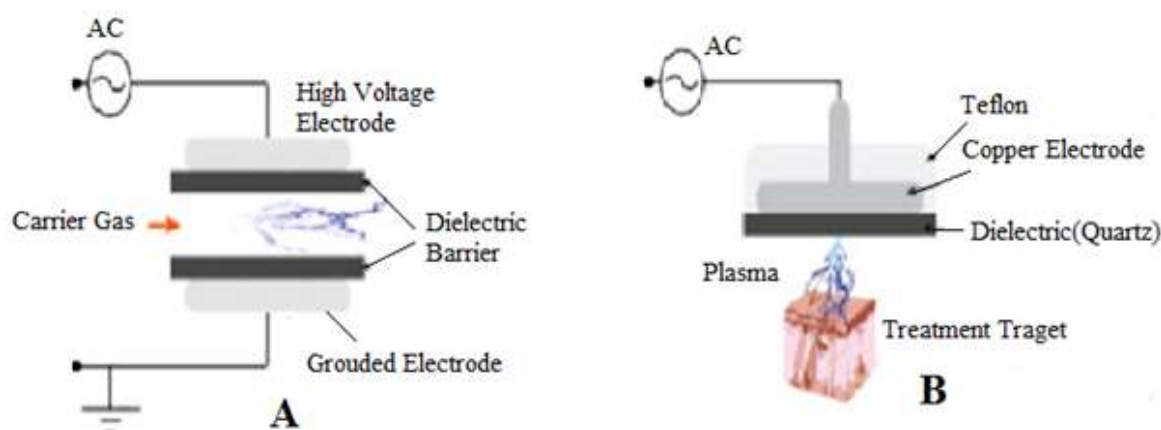


Fig-1: show currently plasma jets that used of DBD system also are produce
A: DBD
B: FE-DBD

Atmospheric plasma jet (APPJ)

RF plasma jet

A plasma jets that are used for sterilization of bacteria is Atmospheric plasma jet (APPJ). APPJ is containing two central electrodes that between the two electrodes is a mixture of gases, including helium, oxygen and etc in high pressure. To create a drain on the central electrode, used the RF (w 100 -50) in 13.56 MHZ and therefore, the active species generated are removed by high velocity from nozzles and it's received to area treated.

Different microorganisms can be used to disable APPJ [26-31]. In 1992 Koynoma et al is produced first RF cold plasma [32]. Cathode in APPJ is contain a needle electrode of tungsten or a special type of steel (stain less) with a diameter of less 1mm that connected to the RF source by the frequency 13.56 MHZ. Needle electrode stand into a quartz tube where is connected anode electrode. Depending on the application, helium or oxygen is combined with various other gases [33].

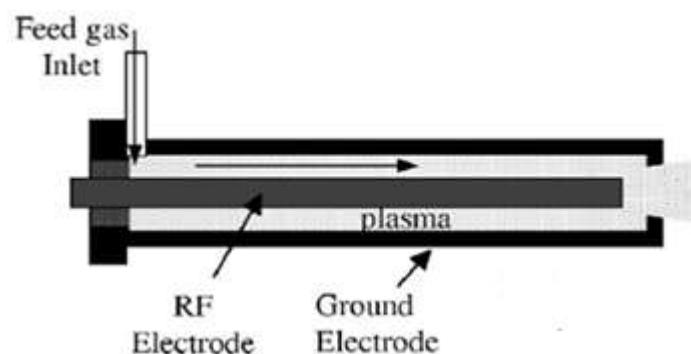


Fig-2: show helium or oxygen is combined with various other gases

Plasma needle:

In 2002 Stoffle et al devised a new plasma jet, which was called the plasma needle, the newer type was produced in 2004 and came to the market [34, 35]. In The old type plasma needle, needle was surrounded by a box, and the samples were stood on box to treatment. The new type, plasma needle has 0.3mm diameter that was surrounded by a metal cover and their sharp peak were stood inside Perspex tube. The needle length was 8cm that 1.5cm was placed out from Perspex tube. Helium gas was used mainly because of the high

thermal conductivity. This gas at the tip where micro-discharges were caused, was synthesized to air [36]. Micro plasma also was generated when the RF, 13.5MHZ and its power was between the 10mw to several watts. In this way the diameter of the plasma under irradiated was 2mm. The small size of this type of plasma, researchers enabled to use from this type plasma in treatment very small part that needed to great care, [37-42]. This type of plasma also were used in disable E-Coli bacteria [43].

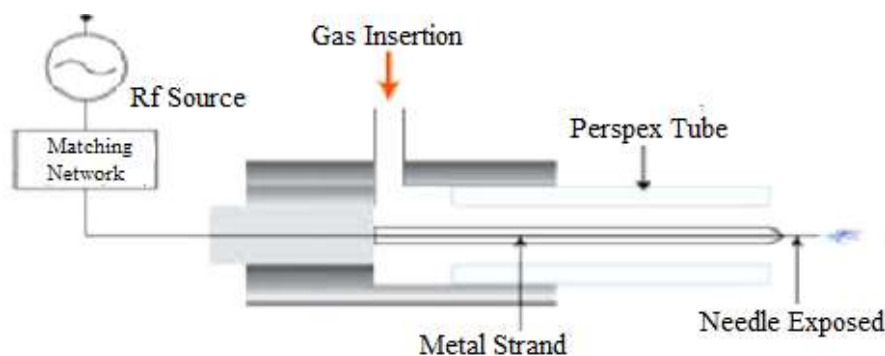


Fig- 3: show Micro plasma

Plasma pencil

In 2005 Laroussi et al used of a thin plasma jet that was called plasma pencil [44]. Plasma pencil includes a dielectric tube diameter cylindrical 2.5cm and two dielectric disk to similar diameter placed inside tube. Two-electrode distance was varies and between 0.3 to 1 cm and consists of a thin copper ring that attached to the disk dielectric. To produce plasma, a high voltage is

applied in gas between the electrodes in microseconds range after the discharge; the plasma plume was shoved from whole outer dielectric into the air. Due to the plasma plume remain in temperatures low 290° K, was easily palpable. Electrode electric power was provided by a generator to high voltage. Plasma pencil was used in the treatment of E-Coli, leukemia and P.Gingivalis [45-47].

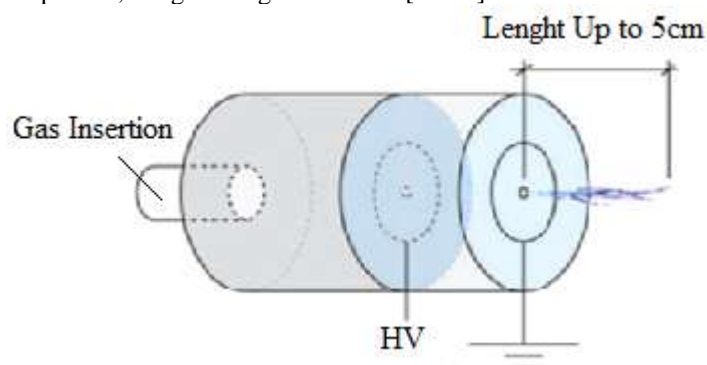


Fig-4: show Plasma pencil

Micro-discharge surface (Surface Micro Discharge): SMD

Micro surface discharge (SMD) is a new technology for production plasma. This technology and that's detail reported in the review Morfill et al [48] and Maisch et al [49]. In this method for producing plasma, electrode was placed at the top of the box. The electrode consists of a Teflon insulation that is surrounded by a network of steel (stain less). High sinusoidal voltage to the 8.5KVp and frequency 1KHZ produced micro-discharges in the network, which was surrounded by air. Energy used for plasma discharge process was 10mw/cm² that was measured by way Lissajon (electrical capacity to the 1μF) [50].

Cold atmospheric plasma applications:

Cold atmospheric plasma used for different biological applications. Studies have shown The CAP is much efficacy in kill germs and sterilization, treatment of wounds and injuries, the material surface changes, hematologic malignancies, organ transplants and treatment of various diseases such as cancer. Other studies also have demonstrated that cold atmospheric plasma can be used successfully to disable bacteria, fungi, viruses, spores, etc [51-57]. In this study we want to examine one of application important cold atmospheric plasma in the oncology.

Cold atmospheric plasma applications in oncology:

In the past few years, atmospheric plasma applications have developed in medicine, such as oncology. Different studies have examined effect of cold atmospheric plasma on cell differentiation, cell migration, apoptosis and necrosis of tumor cells [57].

CAP Molecular mechanisms in cancer cells:

Cell cycle is a series of events that led to the replacement of the cells in the process of division and differentiation. This cycle is consists of 4 different phase: G1, S, G2, M. In this cycle, there are Check Points that control a process of evolution in each of the phases of the cell cycle before the next phase. These points are located in two different points of the cell cycle, one between the S and G2 phases and another in the G2 and M phases. This cell cycle is repeated regularly in all normal body cells. But as we know, cancerous cells have incomplete cell cycle; it seems that the CAP exerts its effect by the impact of on the cell cycle. Many studies about molecular mechanisms of CAP in cancer cells have been done by researchers that in this part we review a number of them.

- Volotskova et-al demonstrated that due to the high percentage of cancer cells are in the S phase of the cell cycle, are very sensitive to the effects of CAP. They found that the CAP delay development of skin cancer cells by stopping the cells in the check point between G2 and M phases. In their study CH2A.X increased that indicates damage to cells in the S phase of the cell cycle [58].

- Tuhvatulin et-al examined mechanism of cell death after treatment with CAP. They observed that the CAP in the treatment of colon cancer cells (HCT115) stimulates the activity of P53 protein and ultimately cell death. They concluded that treatment of human colon cancer cells by CAP leads to the cell apoptosis, which is also dependent on the activity of P53 protein [59].
- Yan et-al found that CAP increases the percentage of apoptotic cells by stopping the cell cycle in M phase and G2. They found that by treatment with CAP, P21CDK expression and P53 protein increases [60].
- Vandamme et-al treated Glioblastoma human cells (U87MG) and human colon carcinoma (HCT-16) by CAP. They observed that CAP is likely to produce large amount ROS (cell death agent). After treatment with CAP, S and M-G2 phases of the cell cycle arrest was observed and DNA damage as a result of treatment was observed one hour after treatment. They concluded that DNA damage in cells treated eventually halts the cell cycle and apoptosis [61]. As well in a in vitro study on mice with human Glioblastoma (U87MG) showed that CAP prevents tumor growth significantly (40%) in the treatment group compared with the control group. They stated that DNA break caused by an accumulation of tumor cells in the S phase of the cell cycle and contributes to the apoptotic cells [62].
- Hak Jan et-al also found that treatment with nitrogen plasma jet by the production of ROS and turns the mitochondria stimulates apoptosis in human cervical cells. They used a jet of air or nitrogen plasma for treatment of human cervical carcinoma (Hela cells). The cells were treated for 2 to 8 minutes. They found that nitrogen and air in the plasma jet in a dose-dependent stimulated apoptosis. ROS levels in Hela cells treated with N₂ and cell striated with plasma jet was 2 and 2.6 times respectively compared with the control group [63].
- Panngom et-al concluded that mitochondria during apoptosis in lung cancer cells that were treated by DBD plasma, may contribute. They in cells treated with CAP, disruption of mitochondrial enzyme activity, morphological changes and cell respiration decreased compared with normal lung cells were treated with plasma observed [64].
- In 2012, Xu et-al investigated the mechanism of action of CAP in cancerous cells. They found that CAP can control the concentration of intracellular ROS, NO and lipid peroxide and showed that the concentration of ROS, NO and lipid peroxide is dependent on liver cell death mechanisms (HepG2) directly. Plasma with production of N₂, increases its concentration in intracellular fluid and due to diffusion process, the concentration of intracellular

ROS increases and ultimately lead to the production of lipid peroxidation and oxidative processes that can damage cells. Combines the ROS, NO and lipid peroxide causes cell death in HepG2. Increasing the concentration of NO, ROS and lipid peroxide during plasma treatment also decreased the viability of HepG2 cells to be [65].

A list of the functions of the CAP mechanisms in cancerous cells:

1. Activating P53
2. Activating inhibitor P21CDK
3. Phase cell cycle arrest at G2 / M and S phase
4. ROS release, DNA damage, cell cycle arrest
5. Stimulating apoptosis through mitochondrial ROS production and turn the mitochondria
6. Decrease in mitochondrial membrane potential, decreases mitochondrial enzyme activity and a decrease in cellular respiration in cancerous cells.
7. The concentration changes of ROS, NO and intracellular fluid lipid peroxide

The main mechanism of CAP in cancerous cells is still unknown. The CAP what's cells stimulates are still not clearly understood but a better understanding of how events stimulated by CAP in cells need to find the optimal dose and good type of plasma in the clinic.

CAP and normal cells:

In the laboratory, several tests on fibroblasts cells, endothelial cells, ovary cells, liver cells and smooth muscle cells were performed. Now briefly turn to the interpretation of these studies.

- Stoffle et-al used a plasma needle in Chinese hamster ovary cells and different results depending on the power and irradiation time observed. The longer the exposure time of 10 s and the power more than 20 w, necrosis, and with less radiation dose plasma, apoptosis was observed and in the amount of approximately 50 mw power and exposure time 1 s, the separation of the cells from the sample, without apoptosis done [66].
- Yonson et al evaluated differentiation of human liver cells after treatment with CAP [67].
- Shashrin et-al used a plasma jet in fibroblast cells and cell differentiation was observed at the intermediate level [68].
- Keift et-al used induced apoptosis in mouse 3T3 fibroblast cells and also in another study used plasma needle for treatment of mammalian endothelial cells and smooth muscle cells [69]. Cell differentiation was observed at lower doses while in higher doses necrosis was created [70]. In this regard, some researchers found that CAP reduces the migration of fibroblasts and epithelial [71].

CAP and malignant cells:

Conventional cancer therapies are chemotherapy or radiotherapy. As regards that some cancers are resistant

to radiation, CAP is one new therapy for the treatment of cancer. So far, different studies have been conducted on the effects of the CAP in killing cancer cells and reduces cell migration and tumor cell sensitivity. Treatment with plasma at low temperatures can cause cell death, including apoptosis and necrosis. In treatment with cold atmospheric plasma, it is assumed that ROS plays a main role. ROS as a harmful factor by stimulating apoptosis, cell cycle arrest is due to sensitivity [72] in this regard Sensing et-al found that ROS is a factor that the CAP due to it stimulates apoptosis [73].

CAP effect on various cancers in vivo environment:

A number of studies regarding the use of CAP by researchers in various cancers in laboratory environments on living organisms have been done. The results of this research are as follows:

In a laboratory study, Fridman et-al used FE-DBD to treat melanoma cancer cells [74]. They observed that apoptosis or necrosis dependent on the therapeutic dose. In melanoma cells treated with low-dose plasma, apoptosis progression was several hours after treatment, while at higher doses, occurs necrosis melanoma cells. Thiagarajan et-al found that the CAP could be due to cell death in leukemia cells (THP-1Cells). They found that treatment with high doses can lead to necrosis, whereas treatment with low doses, stimulates apoptosis [75]. In 2012, Lars Ivo et-al observed that treatment with TTP (Tissue Tolerance Plasma) significantly stimulates apoptosis in pancreatic cancer cells in the laboratory that the effect is very strong in s10 [76].

Walk et-al used the CAP in the treatment of neuroblastoma cells and found that CAP reduces metabolic activity and stimulates apoptosis and decreased cell viability during therapy [77]. Nagendra et-al used cold atmospheric plasma jets in the treatment of brain cancer cells (T98G). They found that the percentage of T98G cell death directly related to exposure time. So that by increasing the plasma exposure time, increased cells death and they found that the plasma prevented from creating colonies in T98G cell mass at all doses [78].

Glioblastoma is a progressive tumor in adults. Treatment with Temozolomide is useful only when the MGMT expression in tumor cells. Koritzer et-al used plasma with SMD technology in the treatment of human GBM cells (LN18, LN229, U87MG). MGMT do not express in U87MG and LN229 cells but expressed in LN18 cells [79].

In a study Temozolomide with CAP were used in the treatment of human glioblastoma cells. In this study it was observed that TMZ alone had no effect on MGMT in fact, initial treatment with CAP increases sensitivity of glioma cells to TMZ, so the combined treatment of CAP for 60 s with 80- 100mM TMZ, significantly

increased cell cycle arrest in M-G2 phases. Barekzi et-al used pencil plasma and helium as the carrier gas in the treatment of leukemia. In this study, CCRF-CEM cells were treated with CAP for min10-0 that a dose-dependent response was observed in cell death. They hypothesized that long-term exposure leads to increased plasma to the deactivation of the sample [80].

Some researchers studies about the effects of CAP in colorectal cancerous cells. They concluded that the CAP significantly prevents progression and the invasion of SW480 colorectal cancerous cells. They also observed that voltage increases plasma better results [81]. Kim et-al used the CAP in the treatment of colorectal cancerous cells (HTC-116). They found that CAP increases cell cycle arrest and apoptosis and leading to a reduction in the progression and invasion of cells [82].

CAP effects on cancerous cells in animals:

Walk and Associates did study on injected neuroblastoma cells in the body mice. Mice injected with Neuro2a cells, were treated with CAP. 7 sample mice received the treatment of CAP for 5 min while 7 mouse control, received no treatment after injection. CAP immediately led to the eradication of the tumor was. However, in some mice, tumor recurrence, but its growth rate was reduced [77]. In another study by Sun et al CAP were used in the treatment of melanoma cells in mice. The results did not show any initial reduction in tumor size, but confirmed the ability of CAP to stop the growth of tumor [83].

Vandamme et-al used FE-DBD plasma in the treatment of mice with U87. They began their treatment when the tumor size on day one or day zero, in the range of 155-145mm³. Infected mice received the plasma 6 minutes daily and within 5 days. On the sixth day they measured tumor volume and observed tumor volume reduction of 56% in the treatment group compared with the control group. The following, long-term effects of treatment with plasma researched and found that the mortality rate decreased in the treatment group by 58%. These results demonstrated the anti-tumor properties of CAP significantly [62].

Kider et-al used a jet of plasma in the treatment of 10 mice with bladder cancer (SCaBER) and 8 mice with melanoma (B16). They observed that in patients with bladder cancer treated with CAP alone for 5 minutes, resulting in the destruction of the tumor. Also found that tumors with an approximate size 5 mm, 2 min treatment with CAP caused the destruction of the tumor as well as larger tumor size is reduced. In treating mice with melanoma found that after treatment with CAP for 5 min tumor growth was significantly reduced and the median survival in the treatment group 5/33 days in the control group 5/24 day [84].

CAP effect on normal and cancerous cells:

Some researchers have found that cancerous cells are more sensitive to the CAP than normal cells so the CAP can be considered as the ideal treatment of cancer. In this section, we review several studies.

Jae Young et-al used a micro plasma jet in the treatment of mice with lung carcinoma (TC-1 fibroblast cells and CL.7 cells). They found more apoptosis in the TC-1 cells compared with CL.7 fibroblast cells treated with the same dose and time of treatment and observed that in experimental conditions, TC-1 cells are much more sensitive than fibroblast cells CL.7 to the plasma treatment. They found that in the specific dose of plasma, apoptosis occurs just in TC-1 cells. This micro plasma can be used in killing TC-1 cells [85]. Kider et-al in vitro examined the effect of the CAP on normal bronchial epithelial cells (NHBE), and lung cancer cells (SW900), melanoma cells and primary macrophages. They observed separation cell of lung cancer cells (SW900) 70-60% while no separation was observed in normal bronchial epithelial cells. Treatment with CAP reduced the number of SW900 cells significantly while the number of NHBE cells remained at the same level. They found that melanoma cells are more sensitive than macrophages cells in the treatment with CAP [84]. Bomi et-al examined effects of plasma jet on metastatic cells (SK-HEP-1) and normal cells (THLE-2) for 2 min. They found that cancerous cells capable of higher separation compared to normal cells after treatment with CAP. According to biochemical and biophysical searches, adhesion of cancerous cells are weaker than normal cells so their responses to CAP are different from normal cells [86].

CONCLUSION

CAP due to its antimicrobial properties and cell death in cells, has a bright future in oncology. In vivo and in vitro studies of CAP in oncology are show that CAP found its solution in the treatment of cancer patients, although further studies are needed to clarify the mechanism of its action.

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