Colon Cancer Therapy Based on Cold Atmospheric Pressure Plasma: 
In Vitro and In Vivo Studies

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Abstract
Colorectal cancer is the second leading cause of tumor-related mortality worldwide. Cold atmospheric pressure plasma has increasingly attracted the attention of scientists and researchers for its ability to remove tumors through selective cell death. In this study, the anticancer effects and mechanisms of plasma-induced apoptosis (direct or indirect helium, and direct or indirect argon plasma) in vitro and in vivo were assessed. The studies demonstrated that all plasma groups effectively induced DNA damage, thus leading to cell cycle arrest with an increase in the G0/G1 phase. Tumoricidal effects on mouse models bearing CT-26 cells revealed significant inhibition of tumor growth. Histological tests showed, tumor growth rates were inhibited significantly by PAM (plasma-activated medium; indirect helium/ or argon) and direct argon plasma. Additionally, the histological score indicated that both direct helium and direct argon resulted in the highest levels of cell death. The application of cold plasma application selectively eradicated cancer and significantly reduced tumor size in vivo without damaging normal cells.

Keywords: Cold atmospheric pressure plasma, Colon cancer, Cell cycle arrest, Apoptosis, Selective targeting therapy.

1. Introductions
Colorectal cancer (CRC) is regarded as the second most common cause of cancer death, accounting for about 10% of global cancer incidence, largely due to current lifestyle and dietary habit as well as insufficient physical exercise. Based on the data published by the American Cancer Society, 153,020 individuals were diagnosed with CRC in 2023, and 52,550 of these individuals will die from the disease [1]. Consequently, there is an urgent need to develop new therapeutic methods and treatments for medical purposes such as cancer [2].

Nowadays, several treatment methods currently exist for cancer. Cold atmospheric pressure plasma (CAP) has found many
applications in medicine, such as cancer treatment (approximately 20 cancer types) [3-7], wound healing and disinfection [8,9], blood coagulation [10], dentistry and periodontal diseases [11,12], organophosphorus or organochlorine pesticide degradation [13], and microbial inactivation [14]. Cancer treatment using CAP has attracted significant attention compared to other conventional modalities due to its cost-effectiveness and reliability. In advanced CAP method, anticancer therapeutic strategies focus on the direct and indirect PAM (plasma-activated medium) treatments, where long-lived reactive species play a role in the indirect CAP treatment. In direct treatment, either short-lived reactive species or physical factors are responsible for treating cancer [15]. CAP, with its energetic electrons, can collide with oxygen and helium gases to create reactive species including nitric oxides, hydroxyl radicals, anion superoxide, alkoxyals, and non-radical species such as hydrogen peroxides, ozone and singlet oxygen [16,17]. Several pathways are responsible for tumor removal under the direct and indirect treatments of CAP.

In vitro and in vivo studies revealed that CAP selectively eradicated cancer cells without damaging normal cells. Tumors’ size reduced remarkably through the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) without any changes to pH and resistance after treatment, decreasing cell migration and inducing cellular apoptosis [18]. The effects of CAP on in vitro and in vivo models were confirmed through the production of ROS and RNS. [19]. Besides ROS and RNS, the researchers investigated the role of myeloid cells and immunogenic cell death to determine possible mechanisms of CAP [20]. The reactive species generated by plasma in the gas phase can interact with cell surface to enter into cell. As a result, they destroy the mitochondrial networks to produce caspases, resulting in activation of apoptotic pathway [21]. In addition, the plasma effect was investigated on colon cancer. Studies demonstrated that proliferation was inhibited through DNA damage and suppression of tumor growth [22,23]. Another pathway is that CAP could be also activated via immune responses to tumor cells, including immune-mediated tumor death and increased macrophage function [24,25]. The selective anti-tumor effects of CAP have also been exhibited in various types of malignant tumors in vitro, such as colorectal carcinoma, leukemia, melanoma, bladder cancer, glioblastoma, lung cancer, thyroid cancer, pancreatic cancer, breast cancer, and head and neck cancers [18,26-30].

A study comparing a human breast cancer cell line (MCF7) with a normal breast epithelial cell line (MCF10A) showed dramatically reduced viability of the cancer cells compared to the normal cells after CAP treatment [31]. Several studies in clinical trials and experimental animal models have evaluated the efficacy and safety of CAP in cancer treatment [4]. The in vivo efficacy of CAP was assessed in treating melanoma cancer, and the tumor growth rate of tumor decreased remarkably [31].

The aim of this research is to assess in vitro and in vivo antitumor effects by CAP-based direct and indirect helium plasma, and direct and indirect argon plasma given their non-aggressive nature, to determine the underlying mechanisms. The experiments included in vitro (the annexin V/PI assay and cell cycle arrest studies) and in vivo (investigation of tumor size, mice weight, and histological analysis) were performed to determine the possible mechanisms.

2. Materials and methods

2.1 Plasma device and plasma treatment methods

In order to treat cancer, two methods were implemented: direct and indirect. In direct method, cell cultures (in vitro) and tumor of
BALB/c mice (in vivo) were directly exposed; in the indirect method, the medium was activated by CAP (also known as PAM) and then transferred to cell lines or injected into tumors in a mouse model. For helium gas, a single-electrode dielectric barrier discharge (DBD) jet was utilized, with the high-voltage electrode consisting of a conductive cylindrical shell placed on a dielectric insulator (quartz).

For argon gas, the jet was in the form of a single electrode, with the high-voltage electrode in the form of a needle placed inside a quartz tube. Both gases were powered by an AC source with a frequency of 20 kHz and a sinusoidal waveform, and a voltage of 4.5 kV. The helium and argon gas flows were set at a flow rate of 2 L per minute, controlled by a mass flow meter [7].

The experimental setup is represented in Fig. 1.

![Experimental setup and treatment methods](image)

### 2.2 Cell culture

CT-26 cell line was purchased from the Cell Bank of Iran’s Genetic Reserve Center (Tehran, Iran). Cells were cultured in Dulbecco’s Modified Eagle’s Medium (DMEM) supplemented with 10% fetal bovine serum, 1% penicillin/streptomycin, and 1% L-glutamine under standard cell culture conditions (37 °C, 5% CO₂ environment, and 95% humidity).

### 3. Experimental Procedure

After culturing the cell line for 24 h, two groups were exposed to direct helium and direct argon plasma for 3 minutes. Meanwhile, in the indirect method, the plasma-activated culture medium (PAM) exposed to helium and argon plasma for three minutes was used and transferred into the cell line to treat the targeted cancer. All experiments were carried out in triplicate wells.

#### 3.1 Apoptosis with the annexin V/PI assay and cell cycle arrest studies

The CT-26 cell lines were seeded at a density of 30×10^6 cells per well on 96-well microplates and incubated in a CO₂ incubator with concentration 5% at 37 °C for 24 h. After the cells adhered to the wells, the cells were treated with direct helium, indirect helium, direct argon, and indirect argon plasma as well as control. Then, the cells were collected and washed twice with pre-cold PBS buffer, resuspended in 5 μg/mL of fluorescence conjugated Annexin V and propidium iodide (PI), incubated in darkness at room temperature for 15–20 minutes, and immediately subjected to analysis using a Coulter Epics XL flow cytometer (BD-FACSCalibur™ Flow Cytometer) to determine the percentage of apoptotic cells. Furthermore, the cells’ cell cycle distribution was analyzed by flow cytometry stained with a
solution containing PI (50 µg/mL) and RnaseA (100 µg/mL).

3.2 In vivo assays

3.2.1 Laboratory animals

The experiment involved a total of 24 rats. Eight-week-old male Wistar rats weighing 20–22 g were purchased from Pasteur Institute of Iran. Animals were housed in Plexiglas cages measuring 23 x 27 x 43 cm, under standard environmental conditions (22 ± 2 °C, with humidity maintained at 45–55%, and 12 h light/dark cycle) with free access to standard water and food intake. All procedures were conducted in accordance with the guidelines for working with laboratory animals, following the principles outlined in the Declaration of Helsinki and were approved by the ethics committee of Shahid Beheshti University of Medical Science (IR.SBMU.CRC.REC.1401.039).

3.2.2 Treatment by CAP: in vivo

Twenty mice were divided into 5 groups; first group: control (n=4), second: direct helium plasma (n=4), third group: indirect helium plasma (n=4), fourth group: direct argon plasma (n=4) and fifth group: indirect argon plasma (n=4). 5 x 10^5 CT-26 cells in a total volume of 5 µL were subcutaneously injected into the mice.

3.3 The investigation of tumor size and mice weight and histological analysis

The size of the tumors was measured using a caliper on the 1st and 7th days before and after the last treatment. Subsequently, the weight evaluation was performed. The tumor tissues of all treated groups were excised for histological analysis. Mice-based BALB/c were anesthetized via intraperitoneal injection a mixture of ketamine (50 mg/kg body weight) and xylazine (5 mg/kg body weight), and prepared for stereotaxic surgery. After separation of the tumor tissue from all mice, the tissues were fixed in 10% formalin for 48 h. They were then dehydrated with alcohol and clarified with xylene. In the next stage, the samples were impregnated with paraffin, and prepared for sectioning. A light microscope (Labomed CxL) was used to analyze Hematoxylin-eosin staining.

3.4 Statistical Analysis

Statistical analysis results were calculated based on three independent experiments as the mean ± standard deviation (range) or a percentage value. Error bars represent standard error of the mean. Statistical analysis was conducted using GraphPad Prism 5 Software (GraphPad Software, Inc., La Jolla, CA, USA). Additionally, p values were denoted as * p < 0.05, ** p < 0.01, *** p < 0.001, and **** p < 0.0001.

4. Results

4.1 Cell Apoptosis

In order to investigate cell death mechanisms and the antiproliferative effects of tumor cells, flow cytometry with annexin V-FITC/PI was used to measure the induction of apoptosis and necrosis.

Based on the results of Fig. 2, the population of necrotic cells for the control, direct helium, indirect helium, direct argon, and indirect argon plasma decreased by 6.32%, 1.54%, 1.09%, 0.154%, and 0.156%, respectively. The proportion of necrotic cells in cell lines treated with plasma was smaller as compared to the control containing CT-26 cell lines. The results obtained from Table 1 and Fig. 2 showed that, in comparison with the control group, cells treated with PAM-based helium or argon and direct argon had the highest toxicity in terms of the sum of early apoptosis. Meanwhile, the cell death treated with direct helium plasma was confirmed via late apoptosis. As shown in Fig. 3a, indirect helium and direct indirect argon plasma treatments induced increasing early
apoptosis. While, the treatment based on indirect helium plasma induced late apoptosis, resulting in a significant decrease the viability of CT-26 tumor cells (sum of early and late apoptosis) in the presence of direct helium and direct argon plasma compared to PAM based on helium and argon plasma (Figs. 3a and b). Furthermore, based on the aforementioned results, all treatments with plasma had considerable toxicity and induced apoptosis, leading to the suppression of CT-26 tumor cell proliferation.

**Table 1.** The obtained results based on the induction of apoptosis and necrosis.

<table>
<thead>
<tr>
<th></th>
<th>Necrotic</th>
<th>Early apoptosis</th>
<th>Late apoptosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>6.32</td>
<td>5.02</td>
<td>11.2</td>
</tr>
<tr>
<td>Direct helium plasma</td>
<td>1.54</td>
<td>29.0</td>
<td>35.1</td>
</tr>
<tr>
<td>Indirect helium plasma</td>
<td>1.09</td>
<td>46.2</td>
<td>42.7</td>
</tr>
<tr>
<td>Direct argon plasma</td>
<td>0.154</td>
<td>57.9</td>
<td>16.1</td>
</tr>
<tr>
<td>Indirect argon plasma</td>
<td>0.156</td>
<td>60.7</td>
<td>19.9</td>
</tr>
</tbody>
</table>

*Fig. 2.* Annexin V-FITC/PI flow cytometric detection of apoptosis in CT-26 cell lines treated with; control, direct helium, indirect helium, direct argon, and indirect argon plasma.

*Fig. 3.* (a): The early apoptosis and late apoptosis (b); Apoptosis rate of CT-26 cell lines treated with direct helium, indirect helium, direct argon, and indirect argon plasma as well as control, **p < 0.01, and *** p < 0.001.
4.2 Cell cycle arrest

Cell cycle arrest is utilized to further explore the mechanism of CAP-induced cancer cell death. DNA histograms can measure cells at a specific cell cycle phase by quantifying their DNA content [32]. The cell cycle distribution was analyzed by measuring DNA content based on flow cytometry with PI staining. According to the results in Fig. 4, the rates of the DNA percentage in Sub-G1 (G0-G1) for the control, direct helium, indirect helium, direct argon, and indirect argon plasma groups were obtained 14.51%, 92.83%, 80.96%, 94.21% and 92.29%, respectively. This indicates that high rates of CT-26 tumor cells treated with plasma were arrested in Sub-G1 phase compared to untreated cells, resulting in reduced growth and inducing apoptosis. Further investigations using flow cytometric analysis showed that plasma treatments enhanced the percentage of apoptotic cells being associated with cell cycle arrest at the G0-G1 phase. Therefore, the results suggest that direct helium, indirect helium, direct argon, and indirect argon plasma have the potential to induce apoptosis in CT-26 cell lines by selectively blocking cancer cells at the G0/G1 cell cycle stage. The results from Figs. 5a-c, obtained from three experiments, suggested that plasma treatment groups were arrested in the cell cycle at G0-G1 phase. Additionally, direct helium, direct argon, and indirect argon plasma induced significant cell cycle arrest at the G0-G1 phase compared to indirect helium plasma [2,33].

![DNA histograms](image)

Fig. 4. Apoptosis measurement based on DNA content and cell cycle analysis of CT-26 tumor cells after direct helium, indirect helium and direct argon CAP treatment as well as without treatment after 24 h.

![Cell cycle histograms](image)

Fig. 5. The histograms of apoptosis measurement in *in vitro* mechanistic studies of the apoptotic pathway in cells (a); G1/G0, (b); S, and (c); G2/M phases.
4.3 In vivo anticancer effects of cold atmospheric plasma

To directly and indirectly validate the effects of CAP on anticancer cells in vivo, 24 syngeneic mouse models bearing CT-26 tumor cells were evaluated and exposed to plasma. Twenty mice were inoculated with CT-26 colon cancer. In the direct groups containing helium and argon plasma, all treated mice received 3 minutes of cold plasma. Meanwhile, in the indirect group, PAM was applied to treat all mice. Tumor growth was monitored for 14 days. Tumor models treated by cold plasma are shown in Fig. 6. Tumor sizes were measured using calipers on days the 1st and 7th days. Additionally, tumor growth inhibition (TGI) was calculated, and tumor sizes (mm$^2$) were measured.

In this study, the size of tumors under direct and indirect treatments of helium or argon plasma on the 7th day decreased significantly compared to the 1st day as shown in Table 2. Meanwhile, in the control group, the tumor size increased on the 7th day compared to the 1st day, indicating a 22.30% increase in size. Consequently a fairly statistically significant increase was also noted in this group. Additionally, tumor growth size decreased significantly by about 21.85% after cold plasma treatment with direct helium plasma on the 7th day (**** p< 0.0001) compared to other groups on the 7th day, as demonstrated in Figs. 5 and 6. On the other hand, tumor growth size of the group treated by using indirect helium plasma reduced by 44.68% on the 7th day compared to the 1st day after treatment with indirect helium plasma (** p < 0.001) (Fig. 7). However, the results showed that colon tumor ablation after treatment on the 7th day for direct (** p<0.01) and indirect (**** p<0.0001) argon plasma treatments decreased by about 30.44% and 31.85%, respectively (Fig. 7), with significant differences observed in the data. The results regarding plasma treatment indicated an improvement in the mice's weight, suggesting the treatment effects of plasma jet. The results confirmed that the indirect helium plasma treatment proved to be the most effective method for treating colon cancer with minimal destructive effects on adjacent nonmalignant cells [34,35].

Fig. 6. Schematic representation of control, direct and indirect groups based on helium or argon plasma in 1st day.

Table 2. The tumor sizes (mm$^2$) for five groups under direct and indirect treatment based on helium and argon plasma in in vivo.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Direct helium plasma</th>
<th>Indirect helium plasma</th>
<th>Direct argon plasma</th>
<th>Indirect argon plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day</td>
<td>1986</td>
<td>2184</td>
<td>2311</td>
<td>2191</td>
<td>2132</td>
</tr>
<tr>
<td>7th day</td>
<td>2429</td>
<td>1208</td>
<td>1806</td>
<td>1493</td>
<td>1483</td>
</tr>
</tbody>
</table>
4.4 Monitoring the weight of mice

The weight results of mice in this study were evaluated on the 1st and 7th days as shown in Fig. 9. Tumor weight dropped considerably by about 29.32% in the control mice group bearing CT-26 tumor cells. After indirect helium-based plasma treatment, the average weight of mice reduced from 22.25 to 21.00 about a 5.6% decrease compared to the control group, which had decreased by about 29.32%. The average weights of other treated groups containing direct helium, indirect argon and indirect argon plasma were reduced by 7.70%, 7.50% and 8.88% respectively, suggesting that plasma treatment could help improve the mice’s weight (Table 3). These methods can help monitor mice during cancer treatment. Additionally, no visible in vivo side effects were observed in any of the groups.

**Table 3.** The mice weight (g) for five groups under direct and indirect plasma treatment based on helium and argon plasma in in vivo.

<table>
<thead>
<tr>
<th></th>
<th>Direct helium plasma</th>
<th>Indirect helium plasma</th>
<th>Direct argon plasma</th>
<th>Indirect argon plasma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st day</td>
<td>22.5</td>
<td>22.25</td>
<td>23.25</td>
<td>22.5</td>
</tr>
<tr>
<td>7th day</td>
<td>20.75</td>
<td>21</td>
<td>21.5</td>
<td>20.5</td>
</tr>
</tbody>
</table>
5. Histology

Microscopical analyses of tumor tissue slices using H&E (hematoxylin-eosin) stained specimens were conducted to demonstrate the tumor cells’ response with a histological evaluation in CAP treatment, providing information about proliferation and induction of cell death via apoptosis. The tumor control group showed an increase in cell generation, reduced apoptosis and a significant rise in tumor volume. In tumor-bearing mouse models treated with CAP, the groups treated with direct argon, and indirect argon exhibited inhibition of new vessel formation in the in vivo, indicating high apoptosis levels through early apoptosis and angiogenesis inhibition. On the other hand, CAP treatment with direct helium plasma demonstrated significant antiangiogenic effects and increased apoptosis as compared to indirect helium plasma treatment in the in vivo. Metastatic lesions were higher in the group treated with indirect argon compared to indirect helium plasma, leading to tumor growth inhibition (see Fig. 10).

Fig. 11, which contains histological score data, demonstrates that the inhibitory effects of CAP treatments were significantly higher than those of untreated animals. The growth-inhibitory effect of direct helium and argon plasma was the most pronounced compared to other CAP treatments. Additionally, direct argon plasma treatment accelerated apoptosis and cell death.

![Histological analyses of tumor tissue slices using H&E stained specimens](image)

Fig. 10. Effects of CAP treatment on histology characterization of tumors induced CT-26 tumor cells in groups-based direct helium, indirect helium, direct argon, and indirect argon plasma stained by hematoxylin and eosin (H&E).

6. Discussion

Surgery, chemotherapy, and radiation therapy, as conventional tumor-targeted cancer therapies, have reduced mortality rates. However, resistance to therapy and treatment costs are among the major challenges to be considered. Notably, plasma therapy provides potentially as a method for practical administration on cancer therapy [36] practical method for cancer treatment.
Cold atmospheric plasma (CAP) jets using helium and argon plasma as direct and indirect carrier gases operating in open air, were used for several selected exposure times. Based on obtained the findings obtained, CAP represents a promising new approach to based on directly target and selectively kill cancer cells [4]. CAP can selectively reduce the number of cancer cells with less destructive effects on adjacent nonmalignant cells [37,38]. The main purpose of this study was to assess the selectivity of plasma-activated media with direct and indirect CAP treatments using helium and argon plasma against CT-26 tumor cells and targeted tumor volumes in vivo using syngeneic mouse models as well as their mechanisms. The results showed inhibition of the growth of colon cancer cell lines (CT-26 tumor cells) and a decrease in targeted tumor volumes in mouse models. Cell death included necrotic or apoptotic processes. Necrosis and apoptosis are typically described as nonspecific and programmed cell death, respectively.

One of the mechanisms of apoptosis activation is DNA damage or lipid peroxidation of the cell membrane, which reduces cell migration and results in programmed cell death, leading to tumor cell destruction in the in vitro, and in vivo [39]. When the ROS generated by plasma could be attached to DNA, resulting oxidized DNA. Consequently, programmed cell death is activated by ROS to induce cell death via the apoptosis pathway and cell cycle arrest leading to tumor cell destruction in the in vitro, and in vivo. Understanding the molecular mechanisms of induced apoptosis was important to determine plasma functions in a cancer cell line. In addition, the reactive oxygen and nitrogen species (RONS) can be regulated apoptosis as key mediators of oxidative damage during plasma treatment [40]. Cell viability decreased by reducing mitochondrial membrane potential due to the accumulation of ROS inside the mitochondria, resulting that the mitochondria-mediated signaling pathway was induced with the release of cytochrome c from mitochondria into the cytosol and subsequently activation of caspase-3-dependent and caspase-7 to create apoptosis [4,41,42]. Accordance with Figs. 2 and 3, the results based on direct helium/ or argon and indirect helium/ or argon plasma confirmed apoptotic stage (almost early apoptosis) as compared with necrotic stage. In addition, the results obtained cell cycle arrest by using Flow cytometric analysis in this study exhibited CAP increased the percentage of apoptotic cells at the G0-G1 phase (Figs. 4 and 5). When P53 as a tumor suppressor gene is enhanced in the response to DNA damage, cell cycle arrest in cell lines were considered, inducing apoptosis. Furthermore, p53-dependent cell cycle arrest is required transactivation of p21 [43-45]. The PAM injection was also able to decrease tumor size and metastatic potential of pancreatic cancer, ovarian and gastric cancer cells [46-49]. However, the results related to PAM in our studies were confirmed based on the previous studies.

In the in vivo study, tumor which weigh mice-bearing MC38 colon cancer cells models treated with CAP treatments were calculated over time. Tumor volumes and weights were reduced by using CAP treatments for 5 minutes and 15 minutes on the day 10 [50]. Additionally, over 15 minutes, a little effect was observed on the normal adjacent tissue. In our work, tumor volumes and weights were lower than for 3 minutes as compared with the previous study by Jung et al. The previous studies about CAP treatment of murine colon tissue ex vivo over 2 min did not show any cytotoxic effects on normal colon cells [45]. Additionally, mice models treated with PAM exhibited a slight weight loss–including the control mice due to tumor treatment [51].

Our results showed that PAM injection based on helium and argon plasma for mouse models bearing CT-26 tumor cells in, both in vitro and in vivo as a promising treatment option for
cancer therapy. This treatment offers the possibility of effectively treating topically localized tumors. As a result, our plasma devices present a promising new approach in colon cancer therapy.

7. Conclusion

This study was designed to assess the ability of direct and indirect cold atmospheric plasma (CAP) treatment based on helium and argon to inhibit the growth of colon cancer cells in vitro and reduce targeted tumor volumes in vivo using syngeneic mouse models. The studies indicated that direct helium, indirect helium, direct argon, and indirect argon plasma effectively induced cell apoptosis via G0/G1. Flow cytometry data showed that all treatments with indirect helium, direct argon and indirect argon plasma were toxic and induced selectivity via selectivity induced early apoptosis against CT-26 tumor cells. In indirect helium plasma treatment, the apoptotic cell death was also confirmed at the late apoptosis stage. Animal studies demonstrated that He-CAP therapy based on indirect treatment accelerated the tumor reduction and apoptosis enhancement. After plasma treatments, mice showed smaller body weight loss compared to the control group. Additionally, histological score for mouse models bearing CT-26 tumor cells showed that direct helium and argon plasma resulted in the highest cell death resulted through apoptosis. Overall, the results showed that cancer cells were selectively eradicated in the in vitro and in vivo by reducing tumor size without damaging normal cells.

Conflict of interest

The authors declare no potential conflict of interest regarding the publication of this work.

References


