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MULTIPLE APPLICATIONS OF COLD ATMOSPHERIC PLASMA IN MEDICINE

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ABSTRACT

Background: Cold atmospheric plasma (CAP) is a partially ionized gas produced at near-room temperature and atmospheric pressure. It has gained significant interest in recent years due to its diverse biomedical applications, especially in oncology, dermatology, and wound healing. The therapeutic potential of CAP is primarily based on the generation of reactive oxygen and nitrogen species (RONS), as well as minor ultraviolet radiation.
Aim: The aim of this review is to summarize current knowledge from 2020 to 2025 regarding the biological effects and clinical applications of CAP, with particular emphasis on its role in cancer treatment, dermatological conditions, and wound management.
Material and methods: A literature review was conducted using the PubMed database, focusing on articles published in English between 2016 and 2025 with a particular focus on recent evidence from 2021 to 2025 that address the medical use of CAP. Studies without full text, control groups, or of poor methodological quality were excluded.
Results: In oncology, CAP demonstrates selective cytotoxic effects against tumor cells by disrupting cellular signaling, inducing oxidative stress, and modulating the tumor microenvironment. Studies report efficacy in cancers such as melanoma, breast cancer, and head and neck tumors. In dermatology, CAP exhibits antimicrobial activity, enhances skin barrier repair, modulates immune responses, and improves transdermal drug delivery. In wound care, CAP supports tissue regeneration by promoting cell proliferation, angiogenesis, and the breakdown of microbial biofilms.
Conclusions: CAP is a promising tool in modern medicine with broad therapeutic potential. Despite encouraging results, further research is necessary to standardize treatment protocols, ensure long-term safety, and optimize plasma devices for clinical use.

KEYWORDS

Cold Atmospheric Plasma, Reactive Oxygen Species, Ultraviolet, Oncology, Dermatology and Wound Healing, Dielectric Barrier Discharge (DBD)

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1. Introduction

Cold Atmospheric Plasma (CAP) is a partially ionized gas, often referred to as the fourth state of matter, composed of free electrons, ions, and neutral particles. When these reactive species come into contact with biological surfaces, they initiate a cascade of effects, from physical interactions—such as the generation of reactive species—to biological responses, including cellular damage and signaling. A key feature of CAP is its ability to generate reactive oxygen and nitrogen species (RONS), including short-lived species such as hydroxyl radicals (·OH), superoxide anion ($\cdot O_2^-$), nitric oxide (·NO), and longer-lived species such as ozone (O_3) and hydrogen peroxide (H_2O_2). Maintaining redox homeostasis attenuates inflammation through two main mechanisms: either by directly increasing the cellular oxidative level to relieve reductive stress or by inducing death in already oxidatively stressed cells through additional oxidative pressure. The biological effects of CAP extend to microbial inactivation by creating pores in microbial cell membranes, damaging their DNA, and leading to their inactivation.[1]

CAP also produces ultraviolet (UV) radiation which contributes to its efficacy in treating various conditions by supporting ROS generation and enhancing oxidative stress. Furthermore, the combination of reactive species and UV radiation stimulates skin regeneration by activating cell migration and tissue repair mechanisms. UV emitted by CAP is low-intensity and localized, typically within safe exposure limits, therefore as studies show it is not a significant source of risk.

Unlike traditional plasmas, which usually operate at high temperatures and reduced pressures, CAP stands out by functioning at temperatures close to room temperature. This characteristic makes it especially

suitable for applications in medicine, where heat sensitivity is a concern. Additionally, CAP's ability to operate at atmospheric pressure eliminates the requirement for vacuum equipment, enabling easy generation and maintenance of plasma in open-air conditions. This feature greatly broadens its practical use in a wide range of environments.[2]

Various systems have been developed for the generation of CAP, each characterized by distinct physical dynamics and chemical profiles. Among the most commonly employed configurations are plasma jets and dielectric barrier discharge (DBD) systems.[3] For gentle treatment of a small sample area, a plasma jet device may be more appropriate, whereas for larger areas requiring more intensive treatment, a dielectric barrier discharge (DBD) device is generally more suitable.[4] Substantial advancements have been made to enhance the therapeutic potential of CAP devices and to optimize them for clinical application. These improvements include increasing the effective tissue penetration depth up to 5 cm, as well as addressing key technical challenges such as high-voltage requirements, the risk of intra-organic discharge, controlled gas flow, and the scalability of plasma probe dimensions.

CAP-based cancer therapy can generally be administered via two principal strategies: direct application of plasma to the tumor site, or an indirect method involving the use of plasma-activated medium (PAM). This method offers a promising alternative for treating tumors located in deeper tissues, where direct plasma exposure is not feasible. [5]

In the face of escalating global health challenges, such as antibiotic resistance, cancer, and impaired wound healing, CAP has emerged as a promising biomedical tool with broad-spectrum applicability.

This review aims to synthesize current findings on the biomedical applications of CAP. By examining both preclinical and clinical evidence, this work highlights CAP's potential to redefine therapeutic paradigms across multiple domains of modern medicine with a particular focus on wound healing, oncology and dermatology.

2. Methods

2.1. Literature Search Strategy

A comprehensive literature search was conducted using major electronic databases including PubMed, Scopus, Web of Science, Wiley Online Library, ACS Publications, and SciFinder. The search combined Medical Subject Headings (MeSH) with relevant free-text terms associated with cold atmospheric plasma in medical applications. Boolean operators (AND, OR) were applied to refine the search, ensuring a balance between comprehensiveness and accuracy. The focus was on retrieving peer-reviewed articles published from 2016 to 2025 with a particular focus on recent evidence from 2018 to 2025.

2.2. Inclusion and Exclusion Criteria

To maintain scientific rigor and relevance, the inclusion criteria encompassed peer-reviewed articles, systematic reviews, meta-analyses, and randomized controlled trials (RCTs) published in English. Studies without available full texts, lacking control groups, or exhibiting poor methodological quality were excluded from consideration. An initial screening of titles and abstracts was undertaken to remove irrelevant records, which was subsequently followed by a full-text evaluation aligned with predefined research questions. The quality of included studies was appraised in accordance with established frameworks, including PRISMA and GRADE guidelines.

2.3. Types of Evidence Included

This review synthesizes evidence from high-level medical research, including randomized controlled trials, systematic reviews, and meta-analyses, focusing on the efficacy of various recovery strategies in sport.

2.4. Timeframe and Language

Only articles published in English within the timeframe of 2016 to 2025 were included.

3. Research results

3.1. Cold Atmospheric Plasma in Oncology: Mechanisms and Therapeutic Potential

Compared with conventional cancer therapies, such as chemotherapy, radiotherapy, or phototherapies, CAP therapy has several unique advantages.

With recent advances in plasma-based technologies, CAP has emerged as a promising therapeutic approach in oncology due to its ability to operate effectively under ambient temperature and atmospheric pressure conditions. The underlying mechanism remains unclear, *in vitro* analyses suggest that CAP exerts its effects through a multifaceted disruption of key oncogenic survival pathways, including redox homeostasis, glycolytic activity, and the PI3K/AKT/mTOR/HIF-1α signaling [6]. A possible explanation is that due to hypermetabolism, cancer cells have a higher basal oxidative level than normal cells. Consequently, cancer cells may reach their cytotoxic oxidative threshold more readily when exposed to supplementary oxidative stimuli, such as reactive oxygen and nitrogen species (ROS/RNS) generated by CAP. [7] RONS can infiltrate tumor cells via aquaporins, whose elevated expression in cancer cells—alongside reduced membrane cholesterol—renders these cells more vulnerable to oxidative stress. [8] Additionally, CAP-generated ultraviolet radiation and electric fields contribute to DNA damage and cell cycle arrest.[9] According to previous literature, there have been abundant both preclinical and clinical investigations, which highlighted the importance of reactive oxygen and nitrogen species in the antitumor activity of CAP therapy across multiple cancer types, including melanoma, breast, head and neck cancer., [10], [11].

3.1.1 Head and neck cancer

Given the worldwide incidence and high mortality associated with head and neck cancers, research on the application of CAP for their treatment remains relatively limited. Recent preclinical and clinical investigations have primarily explored CAP's utility in three key perioperative contexts. Preoperatively, CAP has been studied for its potential to increase tumor sensitivity to treatment. Intraoperatively, plasma jets are being evaluated as adjunctive tools for surgical procedures, functioning similarly to handheld devices or in conjunction with standard surgical instruments. Postoperatively, CAP has demonstrated promise in reducing microbial contamination, enhancing hemostasis, and facilitating tissue regeneration.[12].

In an *in vitro* study, human nasopharyngeal carcinoma Fadu cells, human tongue squamous carcinoma Cal27 cells, human melanoma A375 cells, and human thyroid cancer Hth83 cells were utilized as experimental models. The results demonstrated that CAP modulates several critical molecular pathways associated with head and neck cancers, including the E-cadherin/N-cadherin transition, the glutathione (GSH) redox pathway, metabolic signaling, and the PI3K/Akt/mTOR/HIF-1α axis. These pathways regulate key oncogenic processes such as cell proliferation, migration, invasion, epithelial-to-mesenchymal transition, oxidative stress response, apoptosis, and metabolic adaptation. Furthermore, it was shown that the combination of CAP with chemotherapy drugs (cisplatin) or immune checkpoint blockade (ICB) therapies significantly inhibits tumor progression and extends survival in mice.[13]

3.1.2 Melanoma

Cutaneous melanoma has become a key focus in plasma oncology due to substantial preclinical data, verified safety records, and the superficial nature of primary tumors, which allows for non-invasive and repeatable therapeutic applications. While melanoma cells exhibit significant susceptibility to CAP, the detailed molecular mechanisms underlying CAP-induced apoptosis have yet to be fully clarified. [14] Beyond the well-characterized roles of oxidative stress, DNA damage, and mitochondrial dysfunction in CAP-mediated cytotoxicity, recent investigations have highlighted CAP's impact on protein homeostasis mechanisms. Eukaryotic cells use the unfolded protein response (UPR) to cope with unphysiological amounts of denatured or misfolded proteins [15]. This adaptive mechanism mitigates the burden on protein-folding mechanism by degrading specific mRNAs, suppressing global protein synthesis, and enhancing the expression of molecular chaperones. When these adaptive mechanisms fail to reestablish protein homeostasis or must be maintained over a prolonged period, the UPR initiates apoptotic signaling primarily through the activation of the transcription factor CHOP. CAP has been shown to induce UPR activation in melanoma cells, promoting apoptosis via upregulation of CHOP, increased accumulation of misfolded proteins, and depletion of calcium within the endoplasmic reticulum.[16]

Complementary ex vivo analyses of metastatic melanoma skin biopsies treated with CAP corroborate these findings, revealing a significant elevation in apoptotic markers post-treatment. Additionally, CAP exposure modulates the tumor microenvironment by altering the secretion profile of chemokines and cytokines.

Notably, a marked decrease in vascular endothelial growth factor (VEGF) levels was observed in treated biopsies compared to untreated controls. Given VEGF's critical role in promoting tumor angiogenesis, this reduction may contribute to the suppression of neovascularization, thereby inhibiting tumor progression and metastatic potential.[17]

3.1.3 Breast cancer

Breast cancer (BC) has the highest incidence rate among all cancers worldwide, responsible for almost 2.3 million new cases reported in 2022.[18] Moreover, it stands as one of the most fatal cancer types, emerging as the leading cause of death among women. Recent studies have demonstrated that direct exposure to CAP in breast cancer (BC) disrupts the actin cytoskeleton, leading to morphological changes and downregulation of metastasis-associated proteins, thereby potentially inhibiting tumor dissemination.[19] Another study, which examined two types of breast cancer: estrogen receptor-positive (ER+) and estrogen receptor-negative (ER-), demonstrates that CAP primarily induces cancer cell death through the activation of apoptosis. Apoptotic mechanisms can be categorized into extrinsic pathways, which involve activation of cell surface death receptors, and intrinsic pathways, which are mediated by mitochondrial signals. The intrinsic pathway is regulated by critical apoptosis-related proteins, such as cytochrome c, Bax, and Bcl-2, ultimately leading to the activation of caspase-3. Upon initiation of apoptosis, Bax translocates to the mitochondria, playing a crucial role in the propagation of apoptotic signaling. Conversely, Bcl-2 functions as an anti-apoptotic protein, promoting cell survival and inhibiting apoptosis. The balance between Bax and Bcl-2 expression levels, often represented as the Bax/Bcl-2 ratio, serves as an indicator of the rate of apoptosis induction or suppression. Notably, CAP treatment has been shown to increase the Bax/Bcl-2 ratio in both ER+ and ER- breast cancer cells, implying that CAP-mediated apoptosis is closely linked to the modulation of these proteins and involves the mitochondrial apoptotic pathway. [20]

While further investigation is required to fully characterize these interactions, CAP has been proposed as a potentially effective therapeutic strategy for certain breast cancer subtypes.

3.2. Cold Atmospheric Plasma in Dermatology and Skin Care- Advances and Therapeutic Potential

CAP has emerged as a revolutionary therapeutic technology in dermatology, recognized for its safety, effectiveness, and minimal side effects. It demonstrates substantial antimicrobial properties against bacteria, viruses, and fungi, promotes tissue proliferation and wound healing, and inhibits the growth and migration of tumor cells. [21]

The aforementioned technology not only targets pathological tissues but also positively influences the physiological function of healthy skin. A prospective cohort study demonstrated that treatment with dielectric barrier discharge (DBD) CAP resulted in a significant 24% increase in cutaneous oxygen saturation, with effects lasting for at least eight minutes. Furthermore, capillary blood flow was enhanced by 73%, maintaining elevated levels for approximately 11 minutes. These vascular responses were more pronounced in individuals with a lower body mass index (BMI). Importantly, CAP treatment caused only a modest reduction in skin pH (approximately 0.3 units) without inducing any significant alterations in skin temperature or hydration, underscoring the safety and tolerability of CAP in intact skin.[22]

Antimicrobial properties against a broad spectrum of microorganisms, including bacteria, viruses, and fungi merit consideration. The effectiveness of CAP has been particularly noted in the management of dermatological pathogens. For example, treatment with atmospheric pressure plasma jets has been shown to markedly suppress the growth of *Candida albicans* and *Trichophyton mentagrophytes*, while concurrently reducing their adhesive capacity and pathogenicity in nail infection models. [23]

In addition to its direct antimicrobial effects, CAP exhibits a unique ability to target microbial biofilms—structured communities of microorganisms embedded within a self-produced extracellular matrix—which are notoriously resistant to conventional antimicrobial agents and host immune defenses. The generation of reactive oxygen and nitrogen species (RONS) by CAP plays a critical role in destabilizing biofilm integrity, thereby enhancing microbial vulnerability to elimination. This characteristic is of considerable clinical relevance, particularly in the treatment of persistent or relapsing infections where biofilm formation contributes to therapeutic failure.[24]

Moreover CAP exerts significant immunomodulatory effects, making it a promising therapeutic modality for inflammatory skin conditions. CAP treatment has been shown to enhance the infiltration of key immune cell populations, including $CD8^+$ cytotoxic T lymphocytes, $CD3^+$ T cells, and $CD11c^+$ dendritic

cells—cell types that play essential roles in regulating immune responses and promoting tissue repair. Furthermore, it modulates the expression of pro-inflammatory cytokines, contributing to the attenuation of inflammation and the re-establishment of cutaneous homeostasis.[25]

Another aspect of the discussed technology which deserves attention is its influence on skin barrier function and transdermal drug delivery.CAP induces notable changes in the stratum corneum, specifically targeting its lipid matrix and the structural organization of keratinocytes, which collectively enhance skin permeability and improve the efficacy of topical therapies. CAP has been reported to enhance the transdermal penetration of drugs such as galantamine hydrochloride and cyclosporine. Moreover, by temporarily downregulating E-cadherin expression, CAP facilitates the opening of intercellular junctions, thereby increasing skin permeability. Concurrently, CAP-induced modifications to the lipid composition of the skin may reinforce barrier function, particularly in patients with compromised skin, such as those with dermatitis.[26]

CAP represents a multifaceted therapeutic approach in dermatology with demonstrable effects on microbial eradication, inflammation control, tissue regeneration, barrier function, and drug delivery. Its efficacy is supported by histological, immunological, and clinical data. However, further research is warranted to optimize treatment protocols, standardize device parameters, and conduct long-term safety evaluations. Addressing these challenges will be essential for the broader clinical adoption of CAP in routine dermatological practice.

3.2.1.Advances in Wound Healing Using Cold Atmospheric Plasma

The physiological process of wound healing comprises four well-defined stages: hemostasis, inflammation, proliferation of skin cells, and tissue remodeling. Wounds are typically categorized as either acute or chronic. Acute wounds generally follow a predictable healing trajectory, in contrast, chronic wounds are characterized by disrupted healing, often stalling in the inflammatory phase. These may be further complicated by systemic conditions (e.g., diabetes, venous insufficiency), advanced age, or repeated mechanical trauma.These wounds often fail to progress through the standard phases of healing, presenting a significant clinical challenge and adversely affecting patients' quality of life. [27]

CAP has emerged as a versatile and non-invasive therapeutic approach for enhancing wound repair. It exerts its beneficial effects through multiple mechanisms: exerting antimicrobial activity with its strong ability to disrupt bacterial biofilms, including those formed by multidrug-resistant organisms, stimulating the migration and proliferation of keratinocytes and fibroblasts, and modulating integrin-mediated cell signaling. Additionally, CAP induces the production of nitric oxide (NO), a molecule known to facilitate endothelial cell migration and organization into capillary-like structures, thereby promoting angiogenesis and neovascularization in the wound bed. [28]

Histological investigations have further substantiated these regenerative effects. In two consecutive studies it has been demonstrated that short-term CAP treatment in keratinocyte cell line derived from mice significantly increased epidermal thickness and dermal collagen density. Repeated CAP exposure activated the β-catenin signaling pathway in epidermal cells, resulting in epidermal expansion and enhanced dermal remodeling. [29]

Plasma can be delivered either directly to the wound site or indirectly, and its therapeutic efficacy depends on several parameters. These include the design of the plasma device, duration and frequency of exposure, gas composition and flow rate, jet intensity, distance between the plasma source and tissue, and wound-specific characteristics such as extracellular matrix composition and the presence of exudate. CAP's adaptability allows it to be integrated effectively alongside existing therapeutic modalities. [30]

One case report highlights the treatment of a patient with two second-degree burn wounds (15 cm^2 and 79 cm^2 in area), resulting from contact with boiling oil. The wounds were initially painful and inflamed. Following the first CAP session, a second treatment was administered three hours later. Within 16 hours of the second treatment, the patient reported significant pain relief and the early signs of re-epithelialization were evident, with no indication of bacterial infection. [31]

Clinical evidence suggests that CAP therapy can significantly enhance wound healing outcomes in patients with chronic or nonhealing wounds when used in conjunction with standard care. Weekly CAP applications appear to be both clinically effective and cost-efficient. The growing body of safety and efficacy data supports the integration of CAP into routine wound management, offering a patient- and provider-friendly solution for complex wound care.

Discussion

In oncology, CAP offers a distinctive mechanism of action compared to conventional treatments, targeting tumor cells via disruption of redox homeostasis and key oncogenic signaling pathways. The ability of CAP to induce selective oxidative stress capitalizes on the inherent metabolic vulnerabilities of cancer cells, suggesting a promising adjunct or alternative to current therapies. However, clinical translation remains limited by the need for standardized protocols, optimization of dosimetry, and comprehensive safety assessments, particularly regarding long-term tissue effects and potential off-target damage.

Dermatological applications have demonstrated CAP's broad-spectrum antimicrobial properties, immunomodulatory capacity, and facilitation of skin barrier restoration. These attributes collectively support its integration into the management of infectious and inflammatory skin disorders. Moreover, CAP's enhancement of transdermal drug delivery expands its utility in dermatotherapy, potentially improving therapeutic efficacy while minimizing systemic exposure. Nevertheless, device variability and inconsistent treatment parameters hinder comparability across studies, underscoring the necessity for rigorous standardization.

Wound healing represents one of the most promising clinical arenas for CAP implementation. The technology accelerates tissue repair by promoting keratinocyte and fibroblast proliferation, angiogenesis, and biofilm disruption. Importantly, the clinical evidence indicates significant improvements in both acute and chronic wound outcomes when CAP is used adjunctively with conventional care. Despite these encouraging findings, careful monitoring of treatment duration is imperative. Excessive CAP exposure may induce necrosis or apoptosis, ultimately impairing wound healing and potentially contributing to antimicrobial resistance. This highlights the critical balance between therapeutic benefit and cytotoxic risk, emphasizing the need for precise dosing guidelines tailored to wound type and patient-specific factors.

Conclusions

Cold atmospheric plasma represents a transformative biomedical technology with broad therapeutic potential spanning oncology, dermatology, and wound care. The amassed evidence supports CAP's role in selectively targeting malignant cells, combating microbial infections, modulating immune responses, and promoting tissue repair. However, to fully harness CAP's clinical utility, rigorous standardization of device parameters and treatment regimens, alongside comprehensive safety assessments, are imperative. Future research should focus on large-scale clinical trials and mechanistic studies to refine CAP-based interventions, ultimately facilitating their integration into mainstream medical practice. With continued technological advancements and interdisciplinary collaboration, CAP holds promise as a versatile and effective tool in the evolving landscape of modern medicine.

Disclosures

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REFERENCES

1. Wang, Y., Mang, X., Li, D., Wang, Z., Chen, Y., Cai, Z., & Tan, F. (2022). Cold atmospheric plasma sensitizes head and neck cancer to chemotherapy and immune checkpoint blockade therapy. Frontiers in Oncology, 12, 823999. https://doi.org/10.3389/fonc.2022.823999
2. Khalaf, A. T., Abdalla, A. N., Ren, K., & Liu, X. (2024). Cold atmospheric plasma (CAP): A revolutionary approach in dermatology and skincare. *Clinical Plasma Medicine*, 30, 101430. https://doi.org/10.1016/j.cpmed.2023.101430
3. Khalaf, A. T., Abdalla, A. N., Ren, K., & Liu, X. (2024). Cold atmospheric plasma (CAP): A revolutionary approach in dermatology and skincare. *Clinical Plasma Medicine*, 30, 101430. https://doi.org/10.1016/j.cpmed.2023.101430
4. Yan, D., Sherman, J. H., & Keidar, M. (2017). Cold atmospheric plasma, a novel promising anti-cancer treatment modality. *Oncotarget*, 8, 15977–15995. https://doi.org/10.18632/oncotarget.13304
5. Dai, X., Bazaka, K., Thompson, E. W., & Ostrikov, K. (2023). Cold atmospheric plasma: A promising controller of cancer cell states. *Cancers (Basel)*, 15(7), 1904. https://doi.org/10.3390/cancers15071904
6. Wang, Y., Mang, X., Li, D., Chen, Y., Cai, Z., & Tan, F. (2023). Piezoelectric cold atmospheric plasma induces apoptosis and autophagy in human hepatocellular carcinoma cells through blocking glycolysis and AKT/mTOR/HIF-1α pathway. *Journal of Advanced Research*, 48, 133-144. https://doi.org/10.1016/j.jare.2023.03.005
7. Cao, X., Fang, T., Chen, M., Ning, T., Li, J., Siegel, P. M., Park, M., Chen, Z., & Chen, G. (2023). Trehalose enhanced cold atmospheric plasma-mediated cancer treatment. *Journal of Controlled Release*, 354, 634-644. https://doi.org/10.1016/j.jconrel.2023.04.023
8. Braný, D., Dvorská, D., Strnádel, J., Matáková, T., Halašová, E., & Škovierová, H. (2021). Effect of cold atmospheric plasma on epigenetic changes, DNA damage, and possibilities for its use in synergistic cancer therapy. *International Journal of Molecular Sciences*, 22, 12252. https://doi.org/10.3390/ijms222212252
9. Semmler, M. L., Bekeschus, S., Schäfer, M., et al. (2020). Molecular mechanisms of the efficacy of cold atmospheric pressure plasma (CAP) in cancer treatment. *Cancers (Basel)*, 12, 269. https://doi.org/10.3390/cancers12020269
10. Gay-Mimbrera, J., Garcia, M. C., Isla-Tejera, B., Rodero-Serrano, A., Garcia-Nieto, A. V., & Ruano, J. (2016). Clinical and biological principles of cold atmospheric plasma application in skin cancer. *Advances in Therapy*, 33(6), 894–909. https://doi.org/10.1007/s12325-016-0338-1
11. Dai, X., Bazaka, K., Richard, D. J., Thompson, E. R. W., & Ostrikov, K. K. (2018). The emerging role of gas plasma in oncotherapy. *Trends in Biotechnology*, 36(11), 1183–1198. https://doi.org/10.1016/j.tibtech.2018.06.010
12. Hasse, S., Seebauer, C., Wende, K., Schmidt, A., Metelmann, H. R., von Woedtke, T., & Bekeschus, S. (2019). Cold argon plasma as adjuvant tumour therapy on progressive head and neck cancer: a preclinical study. *Applied Sciences*, 9(10), 2100. https://doi.org/10.3390/app9102100
13. Wang, Y., Mang, X., Li, D., Wang, Z., Chen, Y., Cai, Z., & Tan, F. (2022). Cold atmospheric plasma sensitizes head and neck cancer to chemotherapy and immune checkpoint blockade therapy. *Frontiers in Oncology*, 12, 823999. https://doi.org/10.3389/fonc.2022.823999
14. Zimmermann, T., Staebler, S., Taudte, R. V., Ünüvar, S., Grösch, S., Arndt, S., Karrer, S., Fromm, M. F., & Bosserhoff, A. K. (2021). Cold atmospheric plasma triggers apoptosis via the unfolded protein response in melanoma cells. *Cell Death & Disease*, 12(11), 1039. https://doi.org/10.1038/s41419-021-04253-2
15. Adams, C. J., Kopp, M. C., Larburu, N., Nowak, P. R., & Ali, M. M. U. (2019). Structure and molecular mechanism of ER stress signaling by the unfolded protein response signal activator IRE1. *Frontiers in Molecular Biosciences*, 6, 11. https://doi.org/10.3389/fmolb.2019.00011
16. Zimmermann T, Staebler S, Taudte RV, Ünüvar S, Grösch S, Arndt S, Karrer S, Fromm MF, Bosserhoff AK. Cold atmospheric plasma triggers apoptosis via the unfolded protein response in melanoma cells. Cell Death Dis. 2021;12(11):1039. doi:10.1038/s41419-021-04253-2
17. Bekeschus, S., Moritz, J., Helfrich, I., Boeckmann, L., Weltmann, K. D., Emmert, S., Metelmann, H. R., Stoffels, I., & von Woedtke, T. (2020). Ex vivo exposure of human melanoma tissue to cold physical plasma elicits apoptosis and modulates inflammation. *Applied Sciences*, 10(6), 2080. https://doi.org/10.3390/app10062080
18. Bray, F., Laversanne, M., Sung, H., et al. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 74, 229–263. https://doi.org/10.3322/caac.21834

19. Almeida-Ferreira, C., Rodrigues, F., Marto, C. M., Botelho, M. F., & Laranjo, M. (2025). Cold atmospheric plasma for breast cancer treatment: what next? *Medical Gas Research*, 15(1), 110-111. https://doi.org/10.4103/mgr.MEDGASRES-D-24-00043
20. Aggelopoulos, C. A., Christodoulou, A. M., Tachliabouri, M., Meropoulis, S., Christopoulou, M. E., Karalis, T. T., Chatzopoulos, A., & Skandalis, S. S. (2021). Cold atmospheric plasma attenuates breast cancer cell growth through regulation of cell microenvironment effectors. *Cancers (Basel)*, 13(20), 5111. https://doi.org/10.3390/cancers13205111
21. Khalaf, A. T., Abdalla, A. N., Ren, K., & Liu, X. (2023). Cold atmospheric plasma (CAP): a revolutionary approach in dermatology and skincare. *Journal of Cosmetic Dermatology*, 22(5), 1803–1814. https://doi.org/10.1111/jocd.14875
22. Tan, F., Wang, Y., Zhang, S., Shui, R., & Chen, J. (2023). Plasma dermatology: Skin therapy using cold atmospheric plasma. *Journal of Dermatological Science*, 110(3), 150–160. https://doi.org/10.1016/j.jdermsci.2023.01.005
23. Khalaf, A. T., Abdalla, A. N., Ren, K., & Liu, X. (2023). Cold atmospheric plasma (CAP): a revolutionary approach in dermatology and skincare. *Journal of Cosmetic Dermatology*, 22(5), 1803–1814.
24. Khalaf, A. T., Abdalla, A. N., Ren, K., & Liu, X. (2023). Cold atmospheric plasma (CAP): a revolutionary approach in dermatology and skincare. *Journal of Cosmetic Dermatology*, 22(5), 1803–1814.
25. Khalaf, A. T., Abdalla, A. N., Ren, K., & Liu, X. (2023). Cold atmospheric plasma (CAP): a revolutionary approach in dermatology and skincare. *Journal of Cosmetic Dermatology*, 22(5), 1803–1814.
26. Tan, F., Wang, Y., Zhang, S., Shui, R., & Chen, J. (2023). Plasma dermatology: Skin therapy using cold atmospheric plasma. *Journal of Dermatological Science*, 110(3), 150–160. https://doi.org/10.1016/j.jdermsci.2023.01.005
27. Bolgeo, T., Maconi, A., Gardalini, M., Gatti, D., Di Matteo, R., Lapidari, M., Longhitano, Y., Savioli, G., Piccioni, A., & Zanza, C. (2024). The role of cold atmospheric plasma in wound healing processes in critically ill patients. *Journal of Wound Care*, 33(6), 456–467. https://doi.org/10.12968/jowc.2024.33.6.456
28. Bolgeo, T., Maconi, A., Gardalini, M., Gatti, D., Di Matteo, R., Lapidari, M., Longhitano, Y., Savioli, G., Piccioni, A., & Zanza, C. (2024). The role of cold atmospheric plasma in wound healing processes in critically ill patients. *Journal of Wound Care*, 33(6), 456–467. https://doi.org/10.12968/jowc.2024.33.6.456
29. Tan, F., Wang, Y., Zhang, S., Shui, R., & Chen, J. (2023). Plasma dermatology: Skin therapy using cold atmospheric plasma. *Journal of Dermatological Science*, 110(3), 150–160. https://doi.org/10.1016/j.jdermsci.2023.01.005
30. Bolgeo, T., Maconi, A., Gardalini, M., Gatti, D., Di Matteo, R., Lapidari, M., Longhitano, Y., Savioli, G., Piccioni, A., & Zanza, C. (2024). The role of cold atmospheric plasma in wound healing processes in critically ill patients. *Journal of Wound Care*, 33(6), 456–467. https://doi.org/10.12968/jowc.2024.33.6.456
31. Bolgeo, T., Maconi, A., Gardalini, M., Gatti, D., Di Matteo, R., Lapidari, M., Longhitano, Y., Savioli, G., Piccioni, A., & Zanza, C. (2024). The role of cold atmospheric plasma in wound healing processes in critically ill patients. *Journal of Wound Care*, 33(6), 456–467. https://doi.org/10.12968/jowc.2024.33.6.456