COMPREHENSIVE INVITED REVIEW

Plasma Medicine in Wound Care

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Plasma medicine offers an innovative and advanced physical approach to wound care that uniquely combines wound antimicrobial effects (primary goal) and accelerated regeneration of injured tissue (secondary goal). This review explores its transformative potential in modern medicine, demonstrating how this technology can enhance wound healing, reduce microbial load, and improve clinical outcomes. A certified plasma device provides an add-on technology that has the potential to improve current wound care medical procedures by integrating findings from basic research, preclinical models, and clinical applications. This review underscores the significant role of plasma medicine in transforming wound care practices by bridging fundamental research, preclinical validation, regulatory compliance, and clinical application, paving the way for safer, more effective, and minimally invasive treatment strategies.

Keywords: plasma medicine, wound care, antimicrobial effect, regeneration of injured tissue, certified plasma device, clinical applications

SCOPE OF REVIEW AND ITS SIGNIFICANCE

This review focuses on the emerging role of cold atmospheric plasma (CAP) in wound care, highlighting its physicochemical principles, biological effects, clinical applications, and regulatory landscape. As CAP transitions from preclinical research to certified clinical devices, understanding its therapeutic mechanisms and standardization requirements becomes essential. This review aims to offer a multidisciplinary synthesis for researchers, clinicians, and medical device developers.

TRANSLATIONAL RELEVANCE

CAP bridges fundamental plasma physics and biomedical applications by delivering reactive species that influence cellular signaling, angiogenesis, and microbial inactivation. This review outlines translational progress from *in vitro* and *in vivo* models to clinical trials, supporting CAP's evolution into a viable therapeutic platform. It also addresses the technical barriers that must be overcome for clinical implementation.

CLINICAL RELEVANCE

Chronic wounds impose significant health care burdens. CAP

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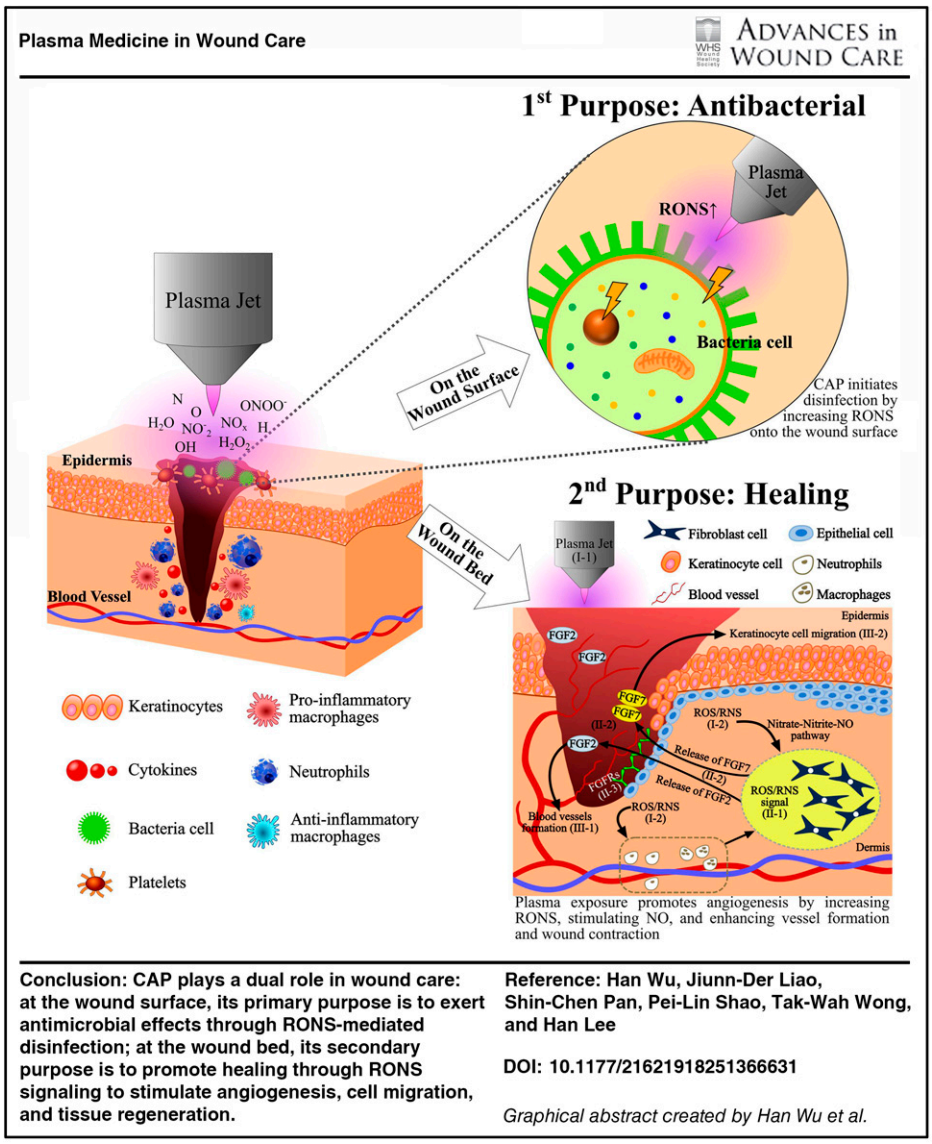


therapy offers a noncontact, nonthermal method to enhance healing, reduce infection, and improve patient outcomes. With growing regulatory clarity and CE-certified devices now in use, this review equips clinicians with up-to-date insights into CAP's practical benefits, safety, and integration into wound management protocols.

INTRODUCTION

Chronic wounds represent a major clinical challenge due to their high prevalence, slow healing rates, and susceptibility to infection. Conditions such as diabetic foot ulcers (DFUs), pressure ulcers, and venous leg ulcers (VLUs) are commonly associated with comorbidities, poor vascularization, and biofilm formation, all of which significantly delay the healing process.[1–3] These wounds impose substantial burdens on patients and health care systems, leading to increased morbidity and treatment costs.[3,4]

Current wound care strategies, such as debridement, topical antiseptics, dressings, and negative pressure wound therapy, offer benefits for certain wound types, but often fall short in managing chronic or infected wounds.[2,5] Persistent microbial contamination and a lack of regenerative stimulation are key limitations, especially in complex wounds or immunocompromised patients.[6,7] As a result, there is a growing need for novel wound therapies that not only suppress microbial burden but also support tissue regeneration. In this context, CAP has emerged as a promising noninvasive

modality. CAP generates reactive oxygen and nitrogen species (RONS), which exhibit both antimicrobial effects and biological activities conducive to wound healing, including angiogenesis and stimulation of skin cell proliferation.[7,8]

Plasma, often referred to as the fourth state of matter, is an ionized gas composed of free radicals, neutral atoms, and charged particles such as electrons and ions.[6,9] It accounts for a small proportion of excited charged particles, but it exhibits unique properties such as conductivity and sensitivity to electromagnetic fields. In 1879, William Crookes first defined plasma as a "radioactive substance," and later, Irving Langmuir introduced the term "plasma." In nonequilibrium states, CAP represents a weakly ionized, low-temperature nonequilibrium state.[5] CAP typically operates at ionization levels below 0.001% and gas temperatures below 100°C, whereas medical applications require temperatures below 40°C.[5,7]

This review is divided into four sections and a concluding outlook. "Understanding CAP for Wound Treatment" section introduces the basic principles of plasma medicine, including generation, key parameters, device types, and historical advances. "Biomedical Applications of CAP" section discusses plasma's antimicrobial and regenerative mechanisms, highlighting its role in oxidative stress modulation and healing acceleration. "Safety Standards and Risk Assessment of CAP" section reviews safety standards and regulatory frameworks, including IEC 60601, DIN SPEC 91315, and ISO 13485, as well as clinical trial requirements for plasma device certification. "CE-Certified CAP Devices in Wound Care Market Trends" section surveys CE-certified plasma devices currently in clinical use, comparing their technical features and clinical performance in treating chronic wounds, diabetic ulcers, and surgical sites. The final section presents a conclusion and outlook on the future of plasma medicine, including comparisons with traditional therapies, its emerging role in esthetic medicine, and the challenges and opportunities in internal applications and treatment standardization.

Understanding CAP for wound treatment

Plasma as the fourth state of matter. Plasma, often described as the fourth state of matter, differs fundamentally from solids, liquids, and gases. It consists of a partially ionized gas containing a dynamic mixture of electrons, ions, neutral particles, and excited species.[9] Despite having only a small fraction of ionized particles, plasma exhibits unique properties such as electrical conductivity, light emission, and responsiveness to electromagnetic fields.[6]

The advancement of plasma technology has enabled its generation under both low-pressure and atmospheric conditions. While low-pressure plasmas have long been applied in the semiconductor industry, atmospheric pressure plasmas have expanded the scope of applications to include surface modification and, more recently, biomedical uses.[5,7] In particular, CAP, a form of low-temperature weakly ionized plasma, has gained increasing attention in the medical field.[7] Its mild operating conditions make it suitable for direct application on biological tissues.[5] CAP emits ultraviolet (UV) and visible light as excited particles return to their ground states, and its unique electromagnetic properties stem from the presence of reactive species and charged particles.[10,11]

Figure 1(a) illustrates the plasma generation process, which transforms matter from solid, liquid, and gas into plasma by adding energy to a gas.[2,12] The main components of plasma (referred to as plasma species) include reactive species such as RONS, UV and visible light, electromagnetic fields, thermal radiation, and excited gas atoms/molecules.[13] RONS refer to a diverse group of biologically active molecules, including reactive oxygen species (ROS) like hydroxyl radicals (•OH), superoxide ($O_2•^-$), and hydrogen peroxide (H_2O_2), as well as reactive nitrogen species (RNS) such as nitric oxide (NO), nitrogen dioxide (NO_2), and peroxynitrite ($ONOO^-$).[14]

In the context of CAP used for wound care, air or controlled mixtures of nitrogen (N_2) and oxygen (O_2) are commonly used as feed gases. These diatomic gases support the generation of a broad range of short- and long-lived RONS in both the gas and aqueous phases, including NO, NO_2, and H_2O_2, which are known to contribute to antimicrobial activity, inflammation modulation, and tissue regeneration.[15,16] This combination of N_2 and O_2 gases enables balanced production of oxidative and nitrosative stress agents, which are essential for effective but controlled biological responses.[14] Therefore, N_2 and O_2 remain the preferred gases for plasma-based biomedical devices. Further discussion on their biological effects is included in "Biomedical Applications of CAP" section.

In biomedical applications, the interaction of these elements produces a nondestructive biological effect that distinguishes CAP from high-temperature plasma treatments.[17,18] CAP requires special attention to plasma temperature, the

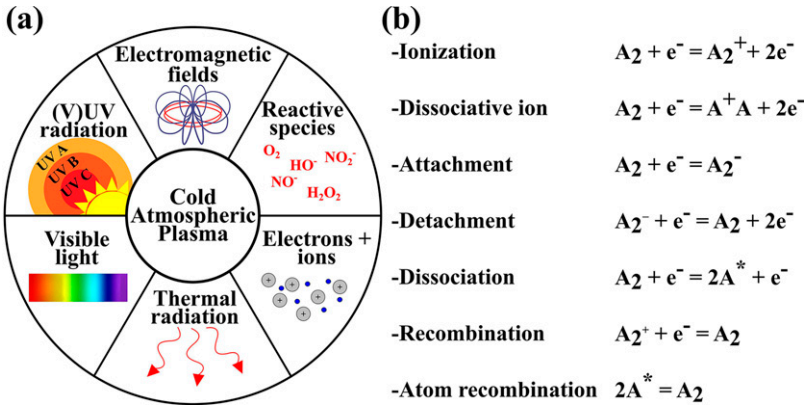


Figure 1. **(a)** Plasma generation involves adding energy to a gas, producing key components for biomedical applications such as reactive species, ultraviolet light, and free electrons.[1] **(b)** Example of excitation of diatomic gas molecule A2 to active species.[1] Schematic created by the authors based on established textbook knowledge.

applied excitation voltage, the controlled levels of RONS, and the type of plasma sources. An overall performance can be validated on an appropriate distance between the plasma source (generating area) and the wound, etc. These parameters are discussed in "Parameters and Types of Plasma Devices for Biomedical Use" section.

Parameters and types of plasma devices for biomedical use. There are at least four main requirements for medical plasma.

First, well-defined CAPs for medical applications should operate within specific parameters to ensure safety and effectiveness. It must produce low temperatures (<40°C) to prevent thermal damage to the skin. The appropriate distance and control parameters between the plasma generation location and the treatment body should be fully verified.[3,19] These parameters are discussed in "Parameters and Types of Plasma Devices for Biomedical Use" and "Criteria for a Reliable Plasma Device in Medicine" section. Note that due to differences in pressure and temperature, plasma states are usually divided into thermal and nonthermal plasma.[20] Thermal plasmas have similarly high-temperature particles, with temperatures at which high-kinetic energy electrons are produced.[20]

Clinical applications such as the PlasmaBlade device leverage controlled thermal plasmas for precision soft tissue dissection. This device, known as the PEAK (Pulsed Electron Avalanche Knife) PlasmaBlade, operates by delivering very brief ($\sim$40 μs), high-frequency pulses of radiofrequency energy to a highly insulated thin electrode, inducing a localized plasma along the blade's edge.[21] By utilizing radiofrequency energy with proprietary insulation technology, the PlasmaBlade achieves precise cutting and coagulation while minimizing thermal injury, making it effective in surgeries ranging from breast oncology to spinal procedures.[21,22] In contrast, nonthermal plasmas such as CAP make electrons much hotter than ions and neutral particles because the electrons have much less mass, resulting in a lower overall plasma temperature.[11] Among them, atmospheric pressure plasmas are particularly interesting due to their ability to operate without expensive vacuum systems, making them ideal for continuous processing applications.[11]

Second, plasma generation involves splitting neutral gas molecules into ionized states according to an applied excitation voltage, where the (required) threshold energy depends on the content of gas molecules per unit volume.[20,23] This process produces a high-energy plasma state in which the disturbed plasma particles can move freely or interact with each other between equilibrium gases, such as energy transfer,[24] to sustain the plasma state for a short period of time. Still, the plasma density will naturally decay exponentially to the ground state.[7] Understanding the energy content and distribution is critical to determining which species will interact with a pathogen, cell, or tissue at a specific location.[7,25]

Third, plasma generates controlled levels of RONS to exert antimicrobial and tissue regenerative effects and be nontoxic to healthy cells. By applying the controlled plasma directly to the wound without the need for complex setup, a CAP can disinfect the wound environment and accelerate healing.[3,19] The main medical effects of CAP include disinfection, promotion of (skin) growth factors, control of (skin) cell migration, and modulation of immune responses,[26] all of which possible applications are related to the generation of

RONS generated by the interaction of plasma with atmospheric species, mainly N_2 and O_2.[27,28] Figure 1(b) lists the possible excited species, taking the excitation of a diatomic molecule as an example. Figure 2 illustrates a plasma plume's multistage reactive species generation and transport process. At phase I, primary reactive species, including electrons, ions, and excited molecules, form within nanoseconds to microseconds. At phase II, as they travel through the afterglow phase over microseconds to milliseconds, secondary species such as O_3 and NO_2 emerge. At phase III, upon reaching biological media, these species interact with liquids and cells, triggering chemical and biochemical reactions lasting from milliseconds to days.[29,30]

Fourth, in plasma medicine, CAP plasma sources encompass a variety of types; however, the most common and commercially available ones are dielectric barrier discharge (DBD) and nonequilibrium atmospheric pressure plasma jet (APPJ).[24] APPJs are particularly advantageous because they can generate stable and controllable plasmas outside a confined area at specific distances. It is highly effective for direct medical applications such as treating diseased tissue.[28] Figure 3(a) and (b) illustrates the general principles of DBD and APPJ, respectively. DBD can produce more uniform and high-density surface discharge, making it suitable for treating irregularly shaped wounds, including those where the surrounding normal skin is also exposed during treatment.[31–33] However, using the wound as another electrode may bring disadvantages in terms of wound management safety.[34,35] APPJ provides more precise 3D wound surface handling capabilities to treat wounds with complex contours or depths.[26] Although APPJ has advantages, attention should be paid to the distance between the plasma and the wound and the treatment time per unit wound during operation. Overall, both technologies still require safety regulations and careful operating procedures and methods when used.[36,37]

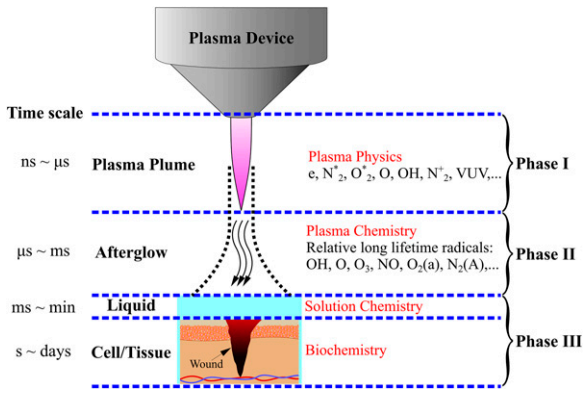


Figure 2. Plasma interactions with target biological tissues span multiple time scales, from the rapid formation of reactive species in phases I and II to prolonged biochemical interactions in phase III, highlighting its complex dynamics in CAP treatment.[30] Redrawn with permission from Lu et al. CAP, cold atmospheric plasma.

As shown in Fig. 2, the combined performance of these three stages will determine the efficiency of the plasma for medical use. The continuous accumulation of plasma species on the wound surface during plasma treatment will affect the performance of plasma-induced wound healing. In addition, various biochemical assessments of wound healing, such as wound contraction or histological sections, would be more helpful for clinical validation.[8]

Criteria for a reliable plasma device in medicine. CAP devices designed for wound treatment are typically classified as Class IIb medical devices, especially when they are intended for use on breached skin over a period exceeding 30 days and their mode of action is primarily physical rather than pharmacological. This classification aligns with precedent cases such as plasma-based skin regeneration devices and surgical plasma beamers, which have been accepted as Class IIb based on their physical mechanism of action and moderate risk profile.[38,39]

Although plasma itself interacts with the wound *via* chemically reactive species (rather than direct device–skin contact), the device that generates plasma remains the regulated object, and its classification depends on its intended use, duration, and invasiveness. The DIN SPEC 91315 standard provides a robust framework for this, offering guidelines for the technical and biological evaluation of plasma sources in medicine.[40] This specification outlines requirements not only for plasma emission and composition but also for safety aspects, such as avoidance of thermal damage and mutagenic risk, emphasizing the need for well-characterized repeatable plasma production and controlled energy delivery.[40,41]

In accordance with Medical Device Regulation (MDR) and ISO 10993 guidelines, Class IIb devices require biocompatibility assessments relevant to their intended use, including cytotoxicity, sensitization, irritation, and systemic toxicity, but not necessarily the full scope of tests applicable to Class III devices such as implants.[42,43] Therefore, our previous mention of ISO 10993 is clarified here to emphasize that only a subset of biological tests is appropriate for our CAP application, guided by its noninvasive nonimplantable nature.[43]

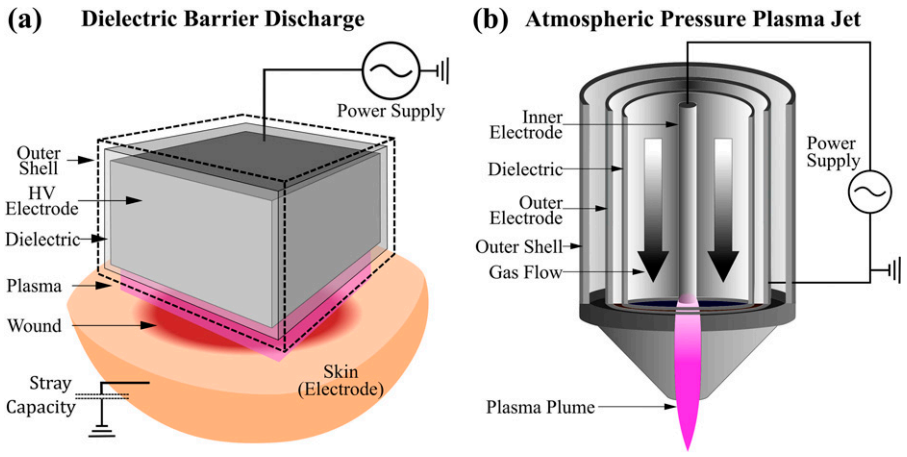


Figure 3. The structural design and operating principles of two common CAP plasma sources. **(a)** DBD structure, which can achieve uniform surface treatment by controlling plasma discharge.[31–33] **(b)** APPJ, whose configuration highlights its ability to precisely target plasma areas.[36,37] Schematic illustration created by the authors based on concepts from multiple sources. APPJ, atmospheric pressure plasma jet; DBD, dielectric barrier discharge.

Furthermore, while academic discussions continue regarding the potential pharmacological aspects of plasma-reactive species, the current regulatory practice in Europe treats CAP for chronic wound therapy as a medical device, due to its physically generated, device-bound mode of action.[39] To ensure clinical safety and reliability, CAP devices must also comply with core technical standards, including IEC 60601-1 (electrical safety), IEC 60601-1-2 (EMC), and appropriate risk management and performance documentation.[44,45] Plasma devices for wound treatment are regulated as Class IIb when their effect is physical, localized, and delivered without direct contact. Relevant requirements are outlined in DIN SPEC 91315 and further addressed in "Safety Standards and Risk Assessment of CAP" section.

Development history of plasma medicine. The history of plasma medicine has its roots in its initial applications in industrial and laboratory settings. Plasma is widely used in a vacuum environment for semiconductor manufacturing and surface modification. These applications involve high-energy plasmas operating at low pressures, which are not suitable for direct use in medical applications due to the specific conditions mentioned above.[28,46]

With the development of CAP, plasma technology has made significant breakthroughs. This innovation enables plasma to be miniaturized and adapted to operate at normal atmospheric pressure and low temperatures, allowing for biomedical applications through *in vitro* and *in vivo* evaluations. Furthermore, through clinical trials for different indications, plasma can be safely applied to living tissue without causing thermal damage, and its effectiveness, such as accelerating wound healing, has also been reported.[19,47] More comments and a literature review will also be given in "Biomedical Applications of CAP" and "Safety Standards and Risk Assessment of CAP" sections.

The first step in exploring the medical potential of plasma is through *in vitro* (cells) and *in vivo* (animals) experiments. These studies demonstrate the dual effects of plasma as follows: effective reduction of microbial load on wounds and stimulation of cellular processes such as proliferation and differentiation.[48,49] With the promising results of preclinical studies, low-temperature plasma devices have been redefined as medical devices requiring rigorous clinical trials (EU Class IIb; US Class III) to determine their safety and effectiveness. This shift marks a critical phase for plasma medicine, with regulatory frameworks and evidence-based approaches driving its integration into health care.[39,50,51]

Over the past decade, plasma devices have become increasingly standardized and commoditized. Devices such as the kINPen® MED[37,52] and PlasmaDerm®[33,53] for minor wounds and Adtec[54,55] for medium-to-large wounds have been developed and approved for clinical use, catering to applications ranging from chronic wound care to pathogen-associated skin diseases. These advancements have established a foundation for plasma medicine as a reliable and accessible therapeutic option.[41,56] A more detailed discussion of these devices and their clinical applications can be found in "CE-Certified CAP Devices in Wound Care Market Trends" section.

Plasma medicine has also been explored in other areas beyond wound care. For instance,

CAP-generated reactive species have shown potential for selective cytotoxicity against tumor cells, with early-stage applications in head and neck cancer and skin malignancies.[57,58] In dermatology, minimally invasive procedures such as skin rejuvenation and scar management have also been investigated.[59,60] However, these remain secondary to the primary clinical focus on wound healing, which is the central scope of this review. A brief overview of these additional applications is included in "Biomedical Applications of CAP" section.

Technical limitations in clinical trials. Although the fundamental principles of CAP are well understood from a physical and engineering perspective, translating them into consistent clinical outcomes remains a significant challenge. Parameters such as voltage, frequency, gas type, and plasma dose are highly device dependent and are usually optimized under laboratory conditions. However, these settings may not reflect real-world clinical variations, such as wound geometry, moisture levels, or patient comorbidities. Furthermore, the biological response to CAP, especially the interaction between reactive species and the complex wound environment, remains incompletely characterized. To move CAP from the laboratory to real clinical use, experts from different fields need to work together to develop clear and practical treatment contexts. These settings must be reliably applicable to different types of wounds and easy for clinicians to apply in real-world care.

Biomedical applications of CAP

Antimicrobial and antisepsis. One of the most significant advantages of plasma is its targeted antimicrobial effect, which can effectively kill bacteria and other pathogens. Plasma produces a variety of active substances, including RONS, which have potent antimicrobial properties. These species destroy bacterial cell walls and membranes, creating a temporarily antiseptic wound environment. Studies have shown that plasma treatment can significantly reduce bacterial loads, even against antibiotic-resistant strains, thereby minimizing the risk of wound infection.[9,61] More broadly, plasma species are effective against bacteria on a variety of tissues, including skin, mucosal surfaces, soft tissues, implant surfaces, and even respiratory and gastrointestinal tissues, making it a versatile infection control tool.[9,62]

In addition to its antimicrobial effects, plasma treatment can improve the wound environment. By disinfecting the wound and cleaning the wound surface, plasma provides a favorable environment for the natural healing process. The reactive species generated by plasma provide transient antiseptic activity and contribute to wound healing, which can also reduce inflammation and accelerate tissue regeneration.[63] It has been shown to be effective in treating various types of wounds, including chronic wounds, diabetic ulcers, burns, and surgical wounds, where controlling infection and enhancing the healing process are critical.[33,63]

RONS in plasma are crucial for cellular responses. These active substances, at controlled concentrations, stimulate cellular signaling pathways involved in wound healing.[64] Literature indicates that RONS play a key role in initiating growth factors and promoting angiogenesis, enhancing fibroblast activity, and increasing keratinocyte proliferation, contributing to faster and more effective wound closure.[65,66] These effects are particularly important in epithelial tissues (such as skin and mucous membranes) and vascular tissue, where they help improve cell proliferation and tissue regeneration. Further discussion will be given in" Bactericidal Mechanism and Tissue Healing Mechanism" section.

Certified plasma devices can achieve these results without causing undesirable cytotoxicity.[41] Overall, appropriate plasma treatment can address infection control and wound repair issues by combining antimicrobial activity with enhanced tissue regeneration. Clinical trial reports show that using plasma to treat chronic wounds can accelerate epithelialization and reduce scarring compared with traditional negative pressure therapy.[67] In addition, plasma treatment protocols often involve shorter and more convenient sessions (*e.g.,* 30 s per application, twice daily), whereas negative pressure wound therapy typically requires longer continuous applications (*e.g.,* 4 h per day), which can be cumbersome in clinical settings.[68] This difference in regimen highlights the potential advantage of plasma treatment in terms of time efficiency and patient compliance.

Bactericidal mechanism and tissue healing mechanism. The CAP discussed here belongs to APPJ, which exhibits potent antimicrobial activity by producing reactive species that destroy key bacterial components. The bacterial cell wall is bombarded by free radicals, causing chemical bonds to break and erode.[69] Lipids and fatty acids undergo membrane lipid peroxidation through the production of superoxide anions and H_2O_2. Nucleic acids, including DNA and RNA, become damaged, leading to reduced cell replication. The cell membrane is damaged and perforated (etched), which promotes

the diffusion of reactive species and causes local damage.[69,70] Proteins and enzymes can undergo denaturation, amino acid oxidation, and enzyme inactivation. These disruptions not only compromise the structural integrity of the bacteria but also increase the biofilm's susceptibility to antibiotics. Gram-negative bacteria are particularly vulnerable due to their thin peptidoglycan layer. CAP is thus a powerful tool to fight microbial infections, complementing its wound healing application by inducing oxidative stress and electrostatic interference.[69,71]

The mechanism of CAP in wound care is to induce cellular processes and promote wound healing by regulating various plasma substances. As shown in Fig. 4(a) and (b), CAP jetting introduces reactive species into the wound environment during the hemostasis phase (a) and initiates the disinfection process (b). On this basis, the various stages of the wound healing process, such as inflammation, proliferation, and remodeling, are shown in Fig. 4(c–e). Neutrophils initiate the inflammatory phase (c) by clearing damaged tissue, paving the way for fibroblast activity in the proliferative phase (d). Subsequently, epithelialization involves the migration of keratinocytes, which ensures wound closure, whereas the remodeling phase (e) strengthens tissue integrity.[72,73] Together, these effects significantly accelerate the wound healing process, highlighting the therapeutic potential of CAP in cellular models.[71,73]

As shown in Fig. 5(a) and (b), CAP treatment shows different biological effects depending on intensity and exposure duration. During wound healing, moderate CAP exposure induces oxidative stress that activates redox signaling and promotes tissue repair in conditions such as chronic wounds, burns, and diabetic ulcers. As shown in (a), these effects may include disinfection, stimulation of cell proliferation, angiogenesis, cell migration, epithelial–mesenchymal transition, and reepithelialization.[7,74]

In contrast, as shown in (b), prolonged or high-intensity CAP exposure can lead to excessive oxidative stress, resulting in apoptosis or necrosis. While such effects have been investigated in other biomedical contexts, including selective effects on abnormal or malignant cells, they may also trigger unwanted processes such as tissue aging, immune reactions, or further cell death. These differentiated responses highlight the importance of precise CAP dosing, particularly in therapeutic applications related to wound healing, which remains the central focus of this review.[74,75]

In vitro *wound healing mechanisms.* Beyond compromising bacterial integrity and influencing cellular stress responses, CAP also modulates growth factors by generating reactive plasma species (RPS), driving key processes in wound healing, as illustrated in Fig. 6(a). This mechanism unfolds in three stages, demonstrating how CAP-induced RPS influences cellular environments to drive wound healing. Unlike conventional single-gas plasmas, using a dual-gas system N_2/Ar microplasma enables the generation of a broader spectrum of RPS. In the first stage, these species are introduced into the cell-containing medium (Stage I-1), increasing RONS levels (Stage I-2) around the cells. The generated RPS includes NO, OH, Ar I, and O, which critically enhance the RONS content.[76]

During the second stage, elevated RONS levels trigger lipid peroxidation and induce LDH leakage from cell membranes (Stage II-1), signifying sublethal damage. Simultaneously, the release of fibroblast growth factor 7 (FGF7) occurs (Stage II-2), aiding membrane repair and supporting essential cell functions such as differentiation.[66,76,77] In addition to FGF7, previous studies have reported that RONS can also upregulate other growth factors such as vascular endothelial growth factor (VEGF), TGF-β, and FGF2, which further contribute to cellular repair and angiogenesis.

In the final stage, FGF7 activates critical signaling pathways, including PI3K/AkT and FRS2-MAPK (Stage III). These pathways enhance cell proliferation (Stage III-1) and migration (Stage III-2), integral to tissue regeneration. The coordinated activation of these and other growth factor-mediated pathways supports the multiphase tissue regeneration process. This process highlights the pivotal role of RONS in stimulating cellular responses that promote CAP-induced wound healing.[78,79]

CAP exerts various biological effects that contribute to its therapeutic potential. The CAP system discussed here is based on an APPJ, which delivers reactive species and UV photons under ambient conditions. Beyond its impact on biofilms, APPJ-type CAP has also been shown to disrupt planktonic bacteria through mechanisms such as membrane perforation, oxidative stress-induced DNA damage, and protein modification.[80] One notable physical mechanism is the etching effect, where charged ions from the plasma disrupt molecular bonds and directly rupture bacterial membranes.[81]

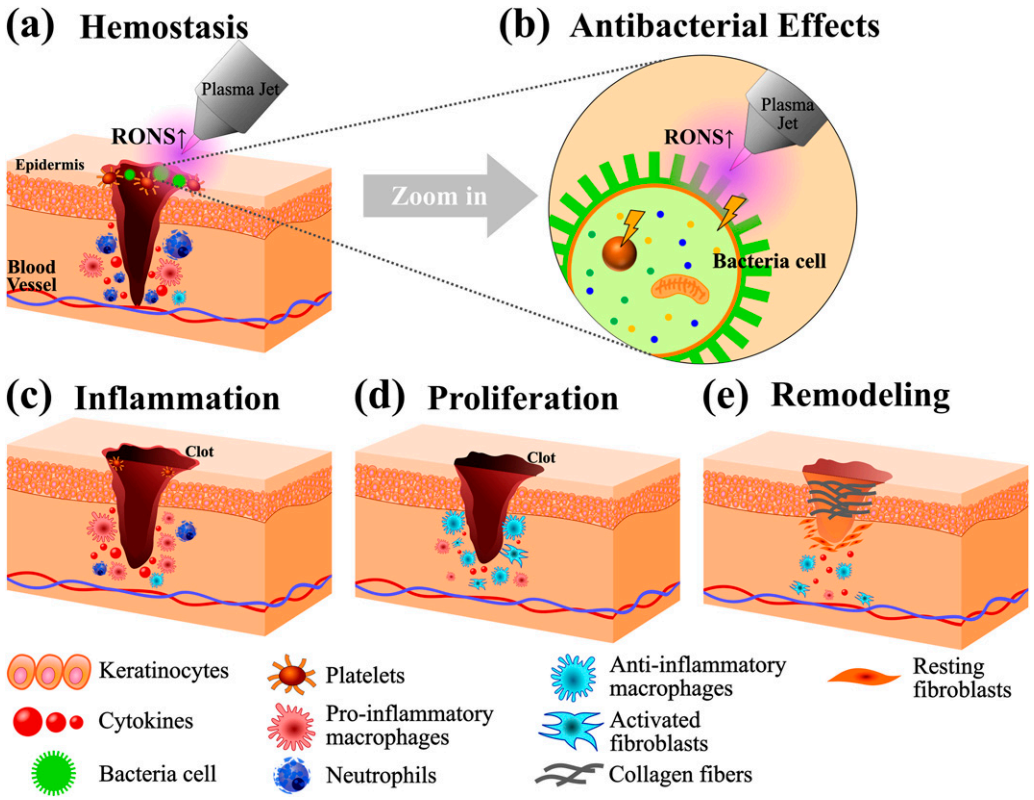


Figure 4. **(a)** Plasma jet releases CAP reactive species during hemostasis. **(b)** The disinfection process initiates, followed by **(c)** inflammation, **(d)** proliferation, and **(e)** remodeling to accelerate the wound healing process.[71] Redrawn with permission from Barjasteh et al.

As illustrated in Fig. 6(b), APPJ-generated CAP interacts with bacterial biofilms in a stage-wise manner. At the onset of exposure, plasma species primarily damage the outermost bacterial layer and the extracellular polymeric substances (EPS). With prolonged treatment, reactive species gradually penetrate into deeper layers of the biofilm, leading to extensive cellular disruption and bacterial inactivation. This depth-dependent disinfection underscores the importance of both biofilm structure and treatment parameters in achieving optimal antimicrobial efficacy.[82]

Another important aspect of CAP's action is its effect on proteins and nucleic acids. CAP exposure alters protein secondary structures by disrupting α-helices and increasing random coil formations, leading to protein misfolding and aggregation.[80] Furthermore, amino acid modifications, such as hydroxylation and carbonylation, promote protein–protein and DNA–protein cross-links, interfering with enzymatic activity and gene transcription. RONS also induce DNA damage *via* single-strand and double-strand breaks, impairing replication and repair processes.[83]

CAP disrupts EPS in bacterial biofilms through oxidation, degrading biofilm structure and reducing bacterial adhesion. In addition, CAP interferes with quorum sensing by degrading signaling molecules such as AHL, disrupting bacterial communication and virulence factor production.[84] However, some bacteria exhibit tolerance mechanisms, including antioxidant enzyme upregulation and biofilm adaptation, where persister cells enter a viable but nonculturable state to withstand CAP-induced oxidative stress.[85] Moreover, CAP has been shown to synergize with antibiotics, enhancing bacterial susceptibility by disrupting membranes and allowing deeper antibiotic penetration. However, at sublethal doses, CAP may also trigger stress responses that promote bacterial persistence and resistance mechanisms.[86]

In vivo *cellular and antimicrobial mechanisms of CAP in wound healing.* *In vivo* studies demonstrated the efficacy and safety of CAP in animal models, which in this context refers to APPJ. For example, studies using rodent models have shown that CAP can accelerate wound healing by enhancing epithelialization and improving the wound microenvironment. These studies revealed no chronic inflammation, necrosis, or adverse cytotoxic effects, solidifying CAP's safety profile. In addition, CAP treatment promoted faster wound closure and

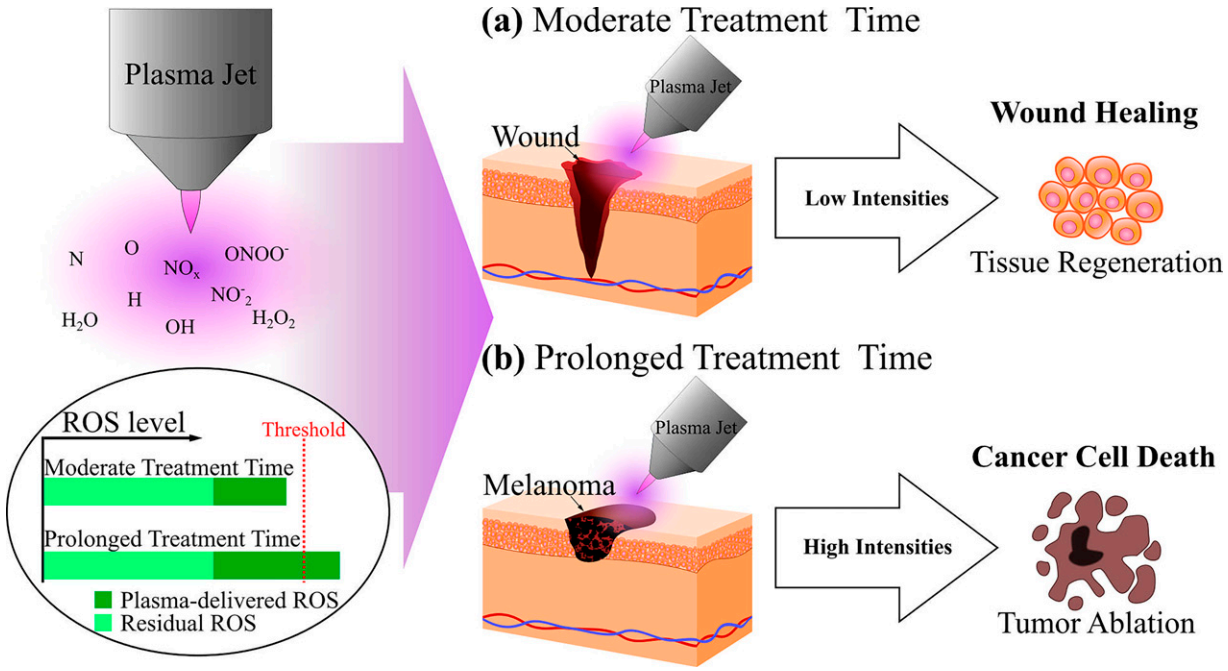


Figure 5. **(a)** Moderate CAP exposure can promote the healing of, for example, chronic wounds, burns, and diabetic ulcers by adding plasma-reactive species that enhance tissue regeneration and antimicrobial effects. **(b)** Prolonged plasma treatment time may significantly accumulate cellular oxidative stress, but on the positive side, it can selectively eliminate cancer cells such as melanoma through apoptosis and necrosis.[74,75] Redrawn with permission from Sies et al. and Keidar et al.

reduced scarring by stimulating cytokine expression and fibroblast migration.[18,87,88]

In addition to these observations, several studies have investigated the safety of CAP on surrounding healthy skin and the wound microenvironment. In a rodent model, high-intensity CAP applied for 30 min caused moderate skin irritation, whereas shorter exposures (10 min or less) showed no observable damage. Even under prolonged low-intensity exposure, skin remained histologically intact with only minimal edema and no significant inflammatory infiltration. CAP also accelerated wound healing in scald models, with treated tissue showing improved skin structure, organized collagen fibers, and restored epidermal layers compared with controls.[89] Supporting evidence from human *ex vivo* studies further indicated that CAP treatment under 60 s did not produce significant histological or ultrastructural skin changes.[90] Therefore, CAP devices should always be used according to recommended exposure times to avoid potential tissue irritation or damage.

Understanding the roles of plasma components in tissues is challenging *in vivo* due to technical limitations. Factors such as electric fields, UV radiation, and ROS interact in complex ways, and tissues act as a "third electrode," complicating studies.[12,91] In addition, plasma effects often involve interactions among diverse cell types, such as macrophages influencing nearby cells *via* inflammatory mediators. Current tools cannot accurately differentiate the oxidative effects of various plasma-derived radicals, leaving the precise role of each component unclear. Despite these challenges, research has advanced understanding, focusing primarily on animal tissues rather than simplified pseudo-tissue models.[12,92]

A study by Ngo et al. explored the *in vivo* mechanisms of plasma exposure by studying nonthermal dual-gas N_2/Ar plasma effects on burn wound healing in mice, focusing on the production of RONS and their impact on angiogenesis and epithelialization. The experiment involved creating second-degree burn wounds on mice using a heated aluminum bar. Healing progression was assessed over 14 days, with H&E-stained sections used to analyze burn depth and tissue regeneration.[93] Plasma exposure significantly accelerated wound healing. Plasma-treated groups showed an early increase in inflammatory responses (days $0 \sim 2$), facilitating initial wound contraction. The RONS signals from plasma enhanced angiogenesis and epithelialization, leading to increased blood vessel formation and thickness. By day 7, plasma-treated wounds had more organized granulation tissue, reduced crusting, and denser vascularization compared with controls. By day 14, they exhibited

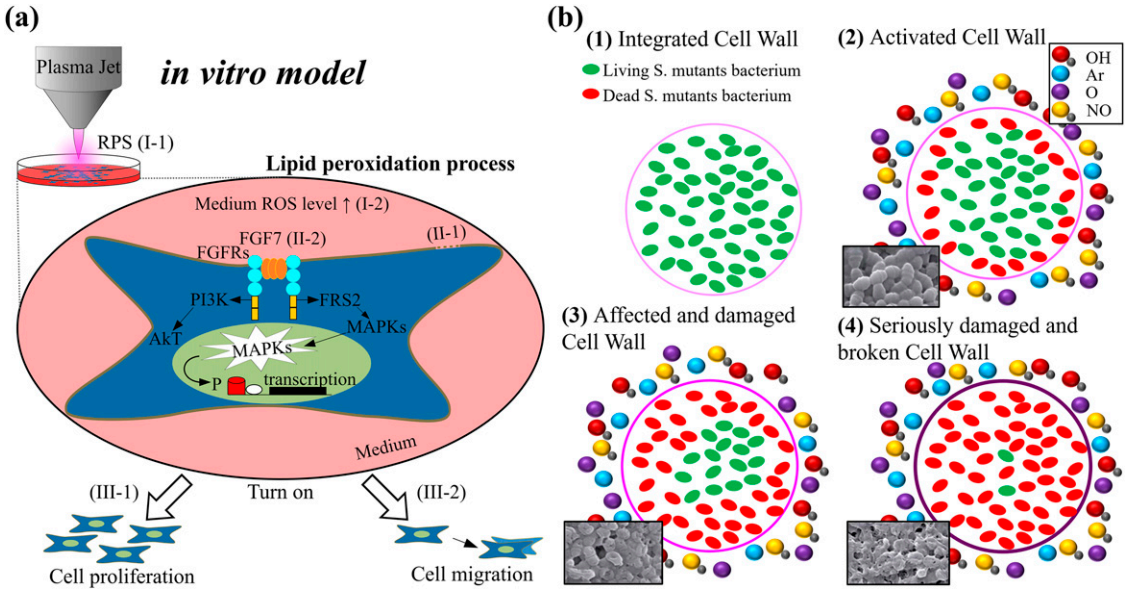


Figure 6. **(a)** RPS generate RONS in the cell-containing medium, leading to LDH leakage and FGF7 release. The released FGF7 activates signaling pathways that promote cell proliferation and migration, contributing to wound healing.[76] **(b)** Proposed mechanism of APPJ-generated CAP acting on dental biofilms. (1) A mature biofilm composed of bacteria and EPS. (2) Initial CAP exposure introduces reactive species and UV light to the biofilm surface. (3) Bacterial cells in the outermost layer begin to exhibit damage. (4) With extended exposure, plasma species penetrate deeper into the biofilm, resulting in widespread bacterial inactivation.[82] Redrawn with permission from Ngo et al. and Huang et al. EPS, extracellular polymeric substances; FGF7, fibroblast growth factor 7; RPS, reactive plasma species; RONS, reactive oxygen and nitrogen species; UV, ultraviolet.

near-complete epithelialization, with a thicker epidermis and more hair follicles, indicating advanced skin regeneration. Quantitative analyses showed significantly faster wound area reduction in plasma-treated groups on days 7 and 14. Based on the study's reported healing timeline, complete wound closure occurred on day 14 for the plasma-treated group and on day 18 for the control group, indicating an approximate 5-day acceleration in healing.[93,94]

Figure 7 depicts the proposed *in vivo* mechanism illustrating how plasma exposure promotes angiogenesis in burn wounds in mice. N_2/Ar microplasma (mark I-1) is applied to the wound tissues, leading to increased concentrations of RONS in the wound bed (mark I-2).[93,95] These elevated RONS levels stimulate NO synthesis in fibroblast cells and macrophages. Continuous oxidation and nitrosation produce nitrites and nitrates, activating the nitrate-nitrite-NO pathway. Nitrite reduction is expected to generate NO radicals, called RONS signals (mark II-1). These signals may promote the release of growth factors FGF2 and FGF7 (mark II-2), which bind to FGF receptors (mark II-3), regulating target genes.[96,97] Consequently, this enhances the formation of new blood vessels in the wound bed and dermal layer (mark III-1) and facilitates cell migration to the wound edges (mark III-2), leading to wound contraction. Overall, angiogenesis is stimulated by blood vessel formation, whereas epithelialization is supported by cell proliferation and migration within the wound bed.[93]

To further elucidate how plasma treatment enhances tissue regeneration, studies have explored the role of nuclear factor erythroid 2-related factor 2 (Nrf2), a key regulator of oxidative stress response, in mediating CAP-induced wound healing effects. The role of RONS in plasma-induced cell stimulation is further enhanced by the activation of Nrf2. Nrf2 is a transcription factor that regulates cellular responses to oxidative stress, which is critical in plasma-assisted wound healing.[98,99] It activates antioxidant genes in response to RONS generated during plasma treatment. Initially bound to Keap1, Nrf2 is released under oxidative stress, translocating to the nucleus to stimulate detoxifying enzymes such as HMOX-1 and NQO1, thereby reducing oxidative stress and controlling inflammation, aiding faster wound healing, particularly in chronic wounds.[99–101] Plasma-induced RONS disrupt the Keap1-Nrf2 complex, activating Nrf2 to regulate oxidative stress, inflammation, and angiogenesis for enhanced wound healing. In addition, Nrf2 influences angiogenesis by regulating factors such as VEGF and inflammatory mediators, ensuring balanced tissue regeneration while remaining safe against tumorigenesis.[98,102]

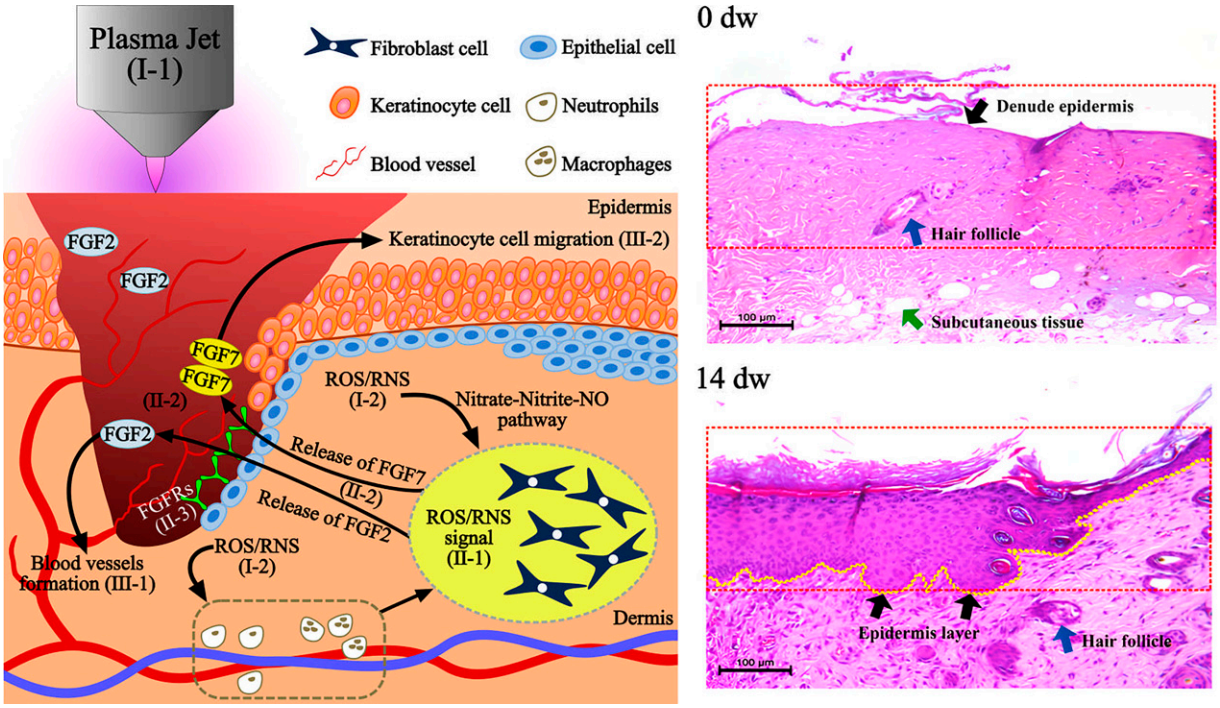


Figure 7. The *in vivo* mechanism of plasma exposure promotes angiogenesis in burn wounds by increasing RONS levels, stimulating NO synthesis, and activating pathways that enhance blood vessel formation, cell migration, and wound contraction. Wound tissue was examined at 0- and 14-days using H&E staining (200X).[93] Redrawn with permission from Ngo et al. NO, nitric oxide; RONS, reactive oxygen and nitrogen species.

CAP has been demonstrated to accelerate wound healing through the generation of RONS. These reactive species influence various cellular processes, including cell proliferation, migration, and differentiation. CAP treatment promotes the formation of new blood vessels, enhances the secretion of connective tissue growth factor and VEGF, and activates the YAP signaling pathway, which plays a crucial role in tissue regeneration.[103] As illustrated in Fig. 8, CAP-mediated wound healing follows a sequence of biological events. Initially, a protective blood scab forms over the injured area. CAP-generated short-lived and long-lived ROS and RNS interact with the wound microenvironment, leading to increased keratinocyte and fibroblast proliferation. In addition, CAP upregulates the expression of critical proteins such as Cx43 and Cyr61, which further facilitate tissue repair and angiogenesis.[104] Moreover, CAP enhances cellular communication between skin fibroblasts and keratinocytes, triggering regeneration signaling pathways that promote wound closure. The ability of CAP to modulate adhesion junctions, cytoskeletal dynamics, and integrin expression further contributes to its wound-healing properties.[8]

Biological challenges in therapeutic use. Although CAP exhibits potent antimicrobial activity and promotes tissue regeneration, its clinical application is still limited due to the lack of standardized treatment protocols. Variations in plasma dose, gas type, duration of treatment, and wound type make comparison of results across studies

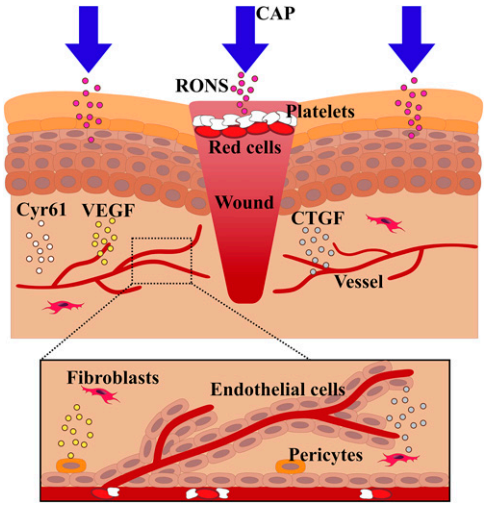


Figure 8. After skin injury, a blood scab forms as the first protective barrier. CAP accelerates healing by generating ROS and RNS, which promote blood vessel formation, enhance CTGF and VEGF release, and upregulate Cyr61 to support tissue regeneration.[8] Redrawn with permission from Zhai et al. CAP, cold atmospheric plasma; CTGF, connective tissue growth factor; ROS, reactive oxygen species; RNS, reactive nitrogen species; VEGF, vascular endothelial growth factor.

difficult. Furthermore, although RONS are essential for therapeutic efficacy, overexposure may cause cytotoxicity and delay healing. Most evidence comes from *in vitro* or small-scale *in vivo* studies, the findings of which may not fully reflect real-world wound dynamics or patient diversity. Therefore, continued clinical research on different indications is still needed.

Notably, while CAP has shown promise in a wide range of wound types, including full-thickness infected wounds, diabetic ulcers, and wounds involving antimicrobial challenges, comprehensive clinical validation in these complex scenarios remains incomplete. Representative studies have reported accelerated healing in full-thickness burn wounds and improved wound closure in diabetic ulcers.[93,105] In addition, CAP has demonstrated notable antimicrobial efficacy in both preclinical and clinical studies.[106,107] However, further clinical trials are needed to confirm efficacy, define treatment parameters, and support wider clinical adoption across these wound categories.

Safety standards and risk assessment of CAP

Safety requirements for medical devices. Plasma medical devices must comply with IEC 60601 standards to ensure safety and reliability. IEC 60601-1 defines the general requirements for basic safety and essential performance, whereas IEC 60601-1-2 regulates electromagnetic compatibility to prevent interference with other medical and electronic equipment. Due to the high-voltage nature of plasma devices, additional safety considerations, such as controlling electric fields, currents, and material insulation, are crucial for compliance.[44]

Plasma devices generate electric fields and charged particles, posing risks if not properly managed. DBDs use the skin as a counter electrode, whereas devices with internal electrode configurations minimize current exposure to biological tissues. IEC 60601 mandates using appropriate dielectric materials, grounding techniques, and shielding to prevent electromagnetic interference and unintended electrical hazards. Compliance testing ensures that plasma devices operate safely under medical conditions, minimizing risks associated with high voltage, leakage currents, and electromagnetic emissions. By adhering to IEC 60601 standards, manufacturers can enhance device safety, regulatory approval, and clinical reliability.[108] Several commercially available plasma devices have been developed in compliance with IEC 60601 standards, including kINPen MED, SteriPlas®, PlasmaDerm, and Plasma Care®. These devices are designed with appropriate insulation, grounding, and electromagnetic shielding to ensure safe clinical application and are discussed in more detail in "CE-Certified CAP Devices in Wound Care Market Trends" section.

Ensuring plasma device safety with DIN SPEC 91315. The physical nature of plasma introduces additional design challenges that intersect directly with safety considerations. Plasma emits a complex mix of components, including RONS, charged particles, UV radiation, heat, and electromagnetic fields, all of which can interact with biological tissues. Excessive UV exposure carries mutagenic and cytotoxic risks, whereas contact with high-voltage components may result in dangerous electric sparks or joule heating.[109,110] Therefore, incorporating dielectric materials and grounded components is critical in the structural design of plasma devices.

DIN SPEC 91315, issued by the German Institute of Standardization in 2014, provides a comprehensive framework for the safe and effective use of nonthermal plasma in biomedical applications. It defines standards for physical properties, including temperature, optical emission spectrum, UV radiation, leakage current, and gas discharge, as well as biological effects such as antimicrobial activity, cytotoxicity, and pH regulation. These guidelines are essential for ensuring the safety of plasma-based medical devices.[40,106] To prevent tissue damage, plasma temperature must be strictly controlled, with measurements taken from the plasma outlet to its generation end point. The standard limits plasma temperature to below 40°C to avoid protein denaturation and impaired wound healing.[41,45] UV exposure is another critical factor, as nonthermal plasma emits radiation across UVA (320–400 nm), UVB (280–320 nm), and UVC (200–280 nm) wavelengths. The maximum daily UV exposure is capped at 3,000 $\mu J/cm^2$, following ICNIRP guidelines.[111,112] Leakage current is regulated under IEC 60601-1 to prevent electromagnetic hazards, ensuring that plasma devices are designed with insulated materials and proper grounding.[44]

Biological and chemical evaluations are crucial for assessing plasma's antimicrobial effects and cytotoxicity. *In vitro* tests using bacterial strains such as *Staphylococcus aureus* and *Pseudomonas aeruginosa* evaluate antimicrobial efficacy through viability assays and growth inhibition tests. In addition, cytotoxicity is measured using MTT/MTS assays to determine the impact of plasma on human cells. Chemical analysis focuses on detecting

RONS, including H_2O_2, nitrite, and nitrate, which serve as key indicators of plasma-induced biological activity.[106,113] However, since these reactive molecules directly influence cellular signaling, inflammation, and wound healing, their concentrations must be carefully regulated. Prolonged or uncontrolled exposure may lead to oxidative stress or damage to lipid bilayers and proteins.

While DIN SPEC 91315 outlines detailed protocols for safety validation, long-term studies remain necessary to fully assess potential risks associated with prolonged or repeated plasma exposure. Such investigations are crucial for refining plasma parameters and expanding their safe application in clinical settings.[114] By integrating physical design considerations with biological and chemical testing, the standard provides a robust foundation for the secure development of plasma medical devices while supporting future innovation and scalability.

Standard for Quality Management System for plasma medical devices. A robust Quality Management System (QMS) is essential for designing, producing, and certifying plasma medical devices. Standards such as ISO 13485 provide a framework for ensuring product safety, risk management, and regulatory compliance. QMS implementation includes design controls, process validation, quality control, and postmarket surveillance, all of which contribute to product reliability and patient safety. Risk management, guided by ISO 14971, is critical in identifying and mitigating potential hazards, including UV exposure, high-voltage components, and RPS. In addition, compliance with Good Manufacturing Practices and international regulatory harmonization efforts ensures that plasma medical devices meet global safety and performance standards. By integrating QMS principles, manufacturers can enhance device efficacy, streamline certification, and maintain high safety standards throughout the product life cycle.[115]

Clinical trials and institutional review board application for CAP devices. After passing safety regulations, plasma medical devices are classified based on their mode of action and risk level to determine whether clinical trials are required. Unlike pharmaceuticals, medical devices are regulated separately in the EU and United States, classified into Class I, IIa, IIb, or III, depending on their invasiveness, duration of use, and potential risks. For example, CAP devices are typically classified as Class IIb medical devices due to their physical mode of action rather than pharmacological effects.[39]

Suppose the competent authority determines that a clinical trial is necessary. In that case, the manufacturer must apply for approval from an institutional review board (IRB), also known as an ethics committee or research ethics board. The primary role of IRB is to protect human subjects in clinical research by reviewing study protocols, assessing risks and benefits, evaluating informed consent procedures, and monitoring ethical compliance.[116] IRB review varies by study risk level, with CAP medical device trials often requiring full board review due to potential risks such as UV exposure, electric fields, and RPS. The IRB evaluates the scientific validity of the study and ensures participant safety. In addition, IRB approval is often necessary for publication, even if a study seems exempt. Given the variability of plasma effects, strict technical validation and real-time monitoring are crucial to maintain consistency, reproducibility, and patient safety throughout clinical trials.[116,117]

Given the variability of plasma effects, rigorous technical validation and point-of-care monitoring are critical to maintaining consistency, reproducibility, and patient safety throughout clinical trials. In addition to the ethical and procedural requirements for IRB approval, regulatory frameworks such as the EU MDR further emphasize the need for clinical evidence to support market authorization and postmarketing surveillance. The MDR requires manufacturers to provide strong clinical evidence, evaluations, and data to demonstrate product safety and performance, ensuring compliance with regulatory requirements and patient safety.[42]

Clinical evidence includes data from clinical trials, scientific literature, and postmarketing surveillance to ensure that devices meet regulatory standards. Clinical evaluation systematically assesses all relevant data to verify the safety and effectiveness of the device. This involves analyzing clinical studies, literature, and real-world performance, culminating in a clinical evaluation report that must be updated regularly. Clinical data include trial results, actual use, and postmarketing surveillance, supporting premarket approval and ongoing monitoring. High-risk devices require postmarket clinical follow-up to ensure ongoing compliance.[42,118] Figure 9 illustrates the relationship between clinical evidence, assessment, and data, emphasizing their roles in regulatory compliance and patient safety. Manufacturers drive innovation in medical technology by maintaining strong clinical evidence, evaluation, and data management to improve regulatory compliance, market competitiveness, and patient safety.

Limitations and challenges in safety and regulation. Although safety standards such as IEC 60601 and DIN SPEC 91315 exist, plasma device manufacturers face challenges in implementing them consistently. Current testing protocols typically emphasize device-level physical parameters, whereas long-term biological safety such as repeated exposure, systemic absorption of active substances, or cumulative UV exposure is insufficiently studied. Furthermore, different regulatory classifications in different regions create barriers to global clinical applications and require harmonization for wider acceptance.

CE-certified CAP devices in wound care market trends

Device selection and experimental setup. CAP technology has become a transformative tool in modern medicine, particularly in the fields of wound healing, dermatology, and cancer treatment. CAP, with its proven antimicrobial effects and ability to stimulate tissue regeneration, offers a promising solution for the treatment of chronic wounds, DFUs, and various skin diseases.[107] Devices such as kINPen MED, PlasmaDerm, SteriPlas, and Plasma Care are currently launched to meet a variety of medical needs products, from local precision treatment to large area wound care. These systems have undergone comprehensive clinical trials to ensure safe and effective integration into clinical practice; further information and comparisons can be found in Table 1.

Although not included in this table, the PlasmaBlade device introduced earlier represents a thermal plasma system that operates *via* pulsed radiofrequency energy for surgical cutting and coagulation. Due to its fundamentally different mechanism and clinical purpose compared with nonthermal CAP devices, it is not listed alongside the wound-healing technologies summarized here.

For researchers seeking to initiate studies in plasma medicine for wound care, careful selection of the appropriate CAP device and thoughtful design of experimental setups are essential to ensure both safety and efficacy. To assist with this process, a schematic decision-making workflow is provided in Fig. 10.

The first step is to identify the type of wound to be addressed. Acute wounds, such as those caused by surgical procedures, and chronic wounds, such as DFUs, differ in their pathophysiology and healing requirements. This distinction is crucial in selecting the most suitable CAP approach.

Once the nature of the wound has been established, the second step is to select a suitable device based on the wound's size and depth. For small- to medium-sized wounds or those with complex geometries, the kINPen MED, an APPJ device using high-purity argon gas, is well-suited. This handheld device allows precise plasma delivery to localized areas, making it ideal for the treatment of DFUs and postsurgical wounds. In contrast, for medium to larger wound areas where broader coverage is required, the SteriPlas device offers a practical solution. This system, also using argon-based APPJ technology, features a multitorch design capable of treating larger surfaces efficiently. For cases where surface-level treatment is the focus, DBD devices such as PlasmaDerm and Plasma Care may be preferred. Both devices operate using ambient air as the plasma source and have demonstrated clinical efficacy in treating a variety of chronic wounds.

The third step is to define appropriate dosage parameters, focusing primarily on plasma exposure time and treatment area. These should be determined based on the wound size and the technical specifications of the chosen device. For example, smaller wounds treated with handheld devices like the kINPen MED typically require 30 ~ 60 s per cm^2, whereas larger wounds using systems such as SteriPlas may need up to 120 s per cm^2. Surface plasma devices such as PlasmaDerm typically require around 90 s per cm^2, whereas Plasma

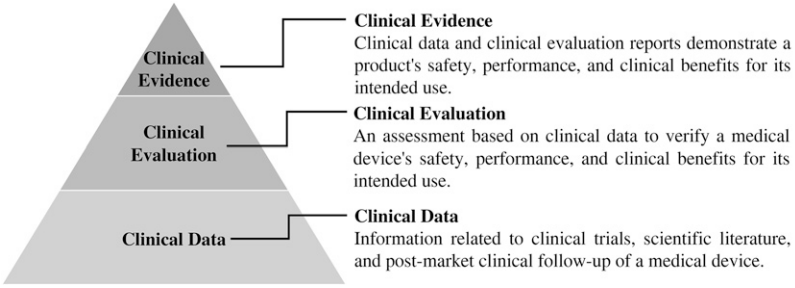


Figure 9. The definitions and relationships of clinical data, clinical evaluation, and clinical evidence for the target medical device in MDR.[42] Figure created by the authors based on information from Regulation (EU) 2017/745, EUR-Lex, accessed May 2025. MDR, Medical Device Regulation.

Table 1. *Comparison of CE-certified cold atmospheric plasma devices, highlighting key features*

Device and Company	*Operating Temp.*	*Gas Flow Rate*	*Treatment Area Size*	*Plasma Type and Gas*	*Clinical Applications*	*Design and Suggested Use*
kINPen® MED (2013, Neoplas Tools GmbH, GER)	ca. 37°C	5 ± 1 SLM	1 cm^2	APPJ (argon, 99.99% purity)	Chronic and acute wounds, inflammatory skin diseases.[37,52]	Handheld, pen-shaped device allowing precise plasma delivery to localized or hard-to-reach areas; ideal for settings requiring targeted treatment.
SteriPlas® (2014, Adtec Plasma Technology, UK)	10°C–30°C	0.5–10 SLM	12 cm^2	APPJ (argon, 99.99% purity)	Chronic and acute wounds, DFUs, surgical infections, dermatology.[54,55]	Multitorch system designed for uniform plasma coverage over larger surface areas; suitable when efficient treatment of broader zones is needed.
PlasmaDerm® (2017, CINOGY GmbH, GER)	Below 40°C	NA	27.5 cm^2	DBD (ambient air)	DFUs, venous ulcers, burns, surgical wounds.[33,53]	Compact, surface-optimized design with integrated electrodes; best suited for applications focusing on superficial and wide-area plasma exposure.
Plasma Care® (2019, Terraplasma Medical GmbH, GER)	ca. 35°C	NA	16 cm^2	DBD (ambient air)	Chronic and acute wounds, bacterial load reduction.[122]	Portable, battery-operated device enabling flexible use in outpatient or home care environments; designed for ease of operation outside hospital settings.

RONS levels increase with longer plasma exposure times and should be considered when determining treatment dosage.
APPJ, atmospheric pressure plasma jet; DBD, dielectric barrier discharge; DFU, diabetic foot ulcer.

Care operates at approximately 3 min for a treatment area of 13 cm^2. Precise dosing helps maximize therapeutic effects while minimizing risks of tissue irritation or oxidative stress.

Finally, step four: To choose experimental model, researchers must determine whether their study focuses on *in vitro* cellular mechanisms or *in vivo* wound healing processes. *In vitro* experiments using cell cultures, such as fibroblasts or keratinocytes, are useful for exploring CAP-induced pathways, including RONS-mediated signaling, proliferation, and migration, and require precise control of exposure time to balance efficacy and cell viability. *In vivo* studies, often using rodent models, are essential for assessing plasma effects on wound healing, including angiogenesis, reepithelialization, and tissue regeneration. In this study, device choice and treatment parameters must match wound size and be carefully adjusted to avoid thermal damage or excessive oxidative stress.

In both experiments, strict adherence to safety standards such as IEC 60601 and DIN SPEC 91315 is vital to control risks from plasma exposure. It is also recommended to use CE-certified devices, including the kINPen MED, SteriPlas, PlasmaDerm, and Plasma Care, which meet established safety and performance requirements for clinical use.

By carefully aligning wound type, device selection, dosage, and experimental model, researchers can build a solid foundation for advancing plasma medicine and strengthening the evidence for CAP in wound care and tissue regeneration.

In addition to wound care, the clinical validation of CAP also extends to adjunctive therapies in other medical disciplines, for example, in dermatology to treat diseases such as psoriasis and onychomycosis, and in oncology to supplement radiotherapy and chemotherapy. The potential in ophthalmology, dentistry, and medical esthetics is also being explored.[119–121] The following sections review their types, availability, and progress in clinical applications.

An example of CAP device for small-to-medium size wound. The kINPen MED is a CE-marked CAP device launched in 2013 for the treatment of infected wounds and inflammatory skin conditions. It uses argon gas to create a focused plasma jet that produces RONS known to inactivate pathogens, stimulate cell proliferation, and improve microcirculation, a key mechanism that supports tissue regeneration.[17] Its small treatment area ($\sim$1 cm^2) and precision make it suitable for complex wound geometries and sensitive areas.[37,52]

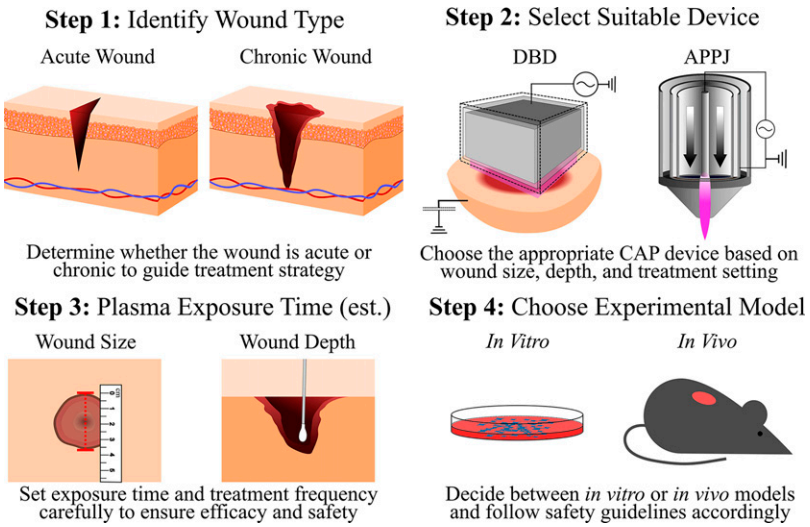


Figure 10. Stepwise decision-making workflow for CAP device selection and experimental setup, including wound type identification, device selection based on wound characteristics, dosage parameter definition, and choice of experimental model.

Its clinical studies have validated its therapeutic potential for chronic wound types, for example: In a randomized, placebo-controlled trial involving 62 wounds in 43 patients with DFUs, CAP treatment resulted in a significant reduction in wound area (–26.31% ± 11.72%, $p = 0.03$) and a shorter clinically relevant healing time ($p = 0.009$) compared with placebo. Although there were no significant differences in the reduction in microbial burden between the groups, no treatment-related adverse events were reported.[105] In addition, a single-center trial comparing CAP therapy with octenidine hydrochloride was conducted in patients with chronic VLUs. After 2 weeks, the wound size in the CAP group shrunk by 39%, significantly higher (negative) than the 12.5% in the octenidine hydrochloride group.[122] Furthermore, a case report of a series of patients who experienced wound healing complications after radial forearm free flap surgery demonstrated complete wound closure in all cases with a mean healing time of 10.1 weeks without infection or adverse events.[123]

These findings highlight the effectiveness and safety of kINPen MED in accelerating the healing of chronic and postoperative wounds. Its antimicrobial and pro-regenerative effects offer a promising adjunct to conventional wound care, particularly in situations where standard treatment is insufficient or antibiotic use must be minimized.

An example of CAP device for medium-to-large size wound. SteriPlas uses a six-electrode system and microwave-driven argon gas to produce CAP.[124] This results in ~ 12 cm^2 treatment area that interacts with the treatment area, significantly reducing the total wound treatment time compared with smaller CAP devices. It has been validated for chronic wounds, DFUs, surgical site infections, actinic keratosis (AK), and other skin diseases.[54,55] The latter disrupts the bacterial cell wall through physical bombardment, electroporation, and RONS activity, leading to bacterial death while sparing mammalian cells.[125]

Clinical trials have verified their effectiveness and safety. A randomized study on chronic wounds showed that weekly treatment reduced wound size by 63%, and treatment thrice a week reduced wound size by 46.8%, while bacterial load decreased by 50.4%.[126] In the DFU examination, a case series of three patients with chronic antibiotic-resistant ulcers reported significant improvement after 8 ~ 11 CAP treatments, with one patient experiencing complete healing and the others experiencing wound stabilization or pain relief.[55,127] Another study found that combining CAP with standard care improved wound healing compared with standard care alone.[128]

For surgical site infections, a study involving 20 patients with driveline infection showed that after 3–15 CAP treatments, several cases were cleared of microorganisms without the need for continued antibiotics.[55] In dermatology, CAP has shown promising results in the treatment of AK. A clinical trial comparing CAP with 3% diclofenac gel in 60 patients with AK showed a significant reduction in the number of lesions (33% vs. 21%) and area affected (41% vs. 27%) in the CAP group, with several patients achieving complete visual

field clearance at follow-up and no side effects reported.[129] Another study on AK also reported improved skin texture and significant clearance of lesions after seven courses of CAP, further supporting the safety and efficacy of CAP as a noninvasive treatment for AK.[130]

These results highlight that SteriPlas can be a versatile noninvasive tool for treating complex wounds and skin diseases.

An example of DBD device for wound care. The PlasmaDerm system uses DBD technology, which utilizes a high-voltage electric field to generate CAP directly on the skin using ambient air. The nonthermal plasma produced by this method can safely interact with tissue and enhance microcirculation and wound healing. It is used to treat acute and chronic wounds, including DFUs, pressure sores, burns, and surgical sites. Reportedly, there is no need to use any additional gas—the skin becomes the balancing pole and, thus, automatically part of the treatment. This creates a unique deep-acting effect that greatly benefits patients and caregivers. Treatment areas range from 1 to 100 cm^2, providing flexibility for both clinical and home care.[33,53]

Clinical studies have shown its ability to promote healing and improve blood circulation. A randomized trial in chronic venous ulcers showed that patients treated with PlasmaDerm thrice a week for 8 weeks experienced enhanced wound healing and antimicrobial effects.[33] In healthy volunteers, a single 90 s application increased blood flow by 73% and oxygen saturation by 24%, with effects lasting up to 11 min. Repeated treatments prolonged these effects, with improved blood flow lasting for more than 13 min.[131]

Optical imaging confirmed improved perfusion after 270 s of treatment, including a 5.1% increase in hemoglobin, a 9.4% increase in oxygen saturation, and a 106% increase in blood flow.[132] In a comparative study, both PlasmaDerm and a spray plasma device were effective in reducing bacterial load on the skin. PlasmaDerm achieved a 1.3 log reduction on physiological skin flora after 210 s of treatment and a 1.7 log reduction on artificially contaminated sites after 90 s of treatment, demonstrating comparable antimicrobial efficacy to the spray plasma system.[133] PlasmaDerm has also been used in transplant conditioning, tumor wound care, and infected amputation sites, demonstrating its broad applicability in wound management and surgical support.

An example of portable DBD device for infection control. Plasma Care is a portable, battery-powered CAP device that uses surface microdischarge technology (a surface DBD) to generate RONS from ambient air.[134] It delivers plasma through a sterile disposable spacer that defines a 16 cm^2 treatment area, allowing for a hygienic and controlled application. It is designed for both acute and chronic wounds to support infection prevention and healing by disrupting microbial structures and promoting tissue regeneration. Its compact design can be used in both outpatient and home care settings, especially for patients with limited mobility. Preclinical studies have demonstrated its safety and no damage to surrounding tissues.[135,136]

Clinical evidence supports its efficacy. A randomized, placebo-controlled, postmarketing clinical follow-up trial with a multigroup multistage design reported a significant reduction in bacterial load with no adverse events, reinforcing its role in infection control.[91,136] Twenty patients went from nonhealing to active healing, with some patients experiencing a 50% reduction in wound size within 4 weeks and some even reporting complete epithelialization of the wound. No pain or side effects were observed, indicating good tolerability and safety in practical use.[136]

Summary of DBD plasma devices in wound management. Two representative DBD-based plasma systems PlasmaDerm and Plasma Care have been developed to support wound healing and infection control using ambient air as the working gas. PlasmaDerm, a clinically established device, is suitable for a wide range of wound sizes and is frequently used in hospital and outpatient settings. In contrast, Plasma Care offers a portable battery-powered alternative with a fixed treatment area, designed for flexible use in home care and mobility-limited patients. Both systems utilize surface plasma discharge to produce RONS and demonstrate antimicrobial effects and enhanced tissue regeneration in preclinical and clinical studies.

Plasma devices in wound care market trends. The global advanced wound care market was valued at $12.9 billion (in USD) in 2024 and is expected to reach $20.2 billion by 2033, growing at a compound annual growth rate of 5.1%. This growth is driven by an aging population, rising prevalence of chronic diseases, and advances in wound care technology. North America is expected to lead the market due to its strong health care infrastructure and demand for innovative treatments.[137]

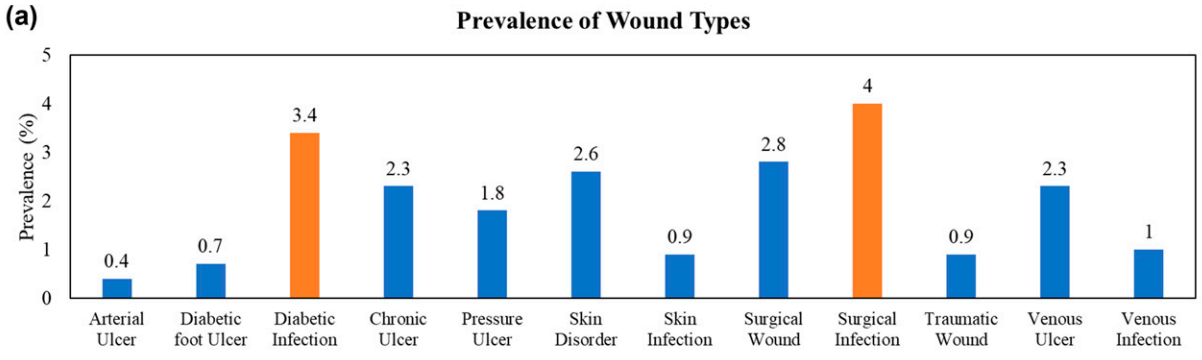
Medicare.gov claims data in 2018 showed that surgical wound infection (4.0%) and diabetic wound infection (3.4%) were the most common wound types, as shown in Fig. 11(a). Its clinical and economic significance is emphasized. Surgical site infections are often caused by complex surgeries, and diabetic wounds, such as foot ulcers, are associated with impaired healing and a high risk of infection. These conditions can significantly increase health care costs and complications, highlighting the need for targeted treatment strategies.[4] Advanced therapies such as plasma therapy are critical to improving treatment outcomes and reducing the burden. Data suggest that innovations in wound care should focus on these high-prevalence categories to achieve the greatest therapeutic and economic impact.[20]

The need for specialized care for chronic wounds was further emphasized.[138] Among 7,099 wounds in 5,240 patients, chronic wounds were the most common (79.0%), with pressure ulcers (23.0%), nonhealing surgical wounds (20.9%), and DFUs (13.7%) being the most widespread. Traumatic wounds (19.2%) and venous ulcers (7.8%) also represent significant challenges, as shown in Fig. 11(b).[138,139] Treating these conditions with advanced modalities such as plasma therapy could significantly reduce their medical burden.

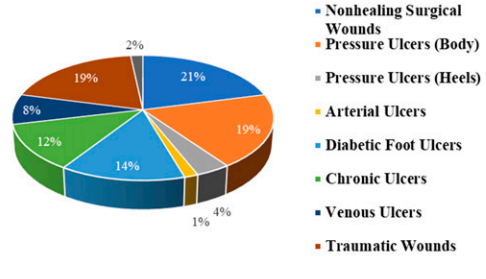
Recent clinical advancements of CAP in wound care. Table 2 summarizes recent CAP-related studies, organized by chronic and acute wound applications, emphasizing clinical presentation, safety, and real-world outcomes.

Recent systematic analyses confirm the growing interest and therapeutic potential of CAP in dermatology. A review written by Gan et al. in 2021 compiled 166 studies. The study concluded that CAP has good promise as a new treatment modality for a variety of skin conditions, including chronic wounds, melanoma, psoriasis, atopic eczema, AK, and pruritus. This review highlights the antimicrobial, anti-inflammatory, and pro-apoptotic effects of CAP, as well as its ability to enhance drug delivery and exhibit good skin compatibility. Although the molecular mechanisms remain to be fully elucidated, the dermatological application of CAP is steadily advancing toward clinical implementation.[140] Together, these observations support the continued integration of CAP into clinical wound care and highlight the need for well-designed trials to validate its safety and effectiveness over time.

As CAP progresses in clinical use in dermatology, ensuring its long-term safety becomes increasingly



(b) Wounds That Require Specialized Care



Wound Type	Percentage (%)	Chronic Wound	Diabetes-Related
Nonhealing Surgical Wounds	20.9	Yes	No
Pressure Ulcers (Body)	19.2	Yes	No
Pressure Ulcers (Heels)	3.8	Yes	Possibly (Vascular)
Arterial Ulcers	1.5	Yes	Possibly (Vascular)
Diabetic Foot Ulcers	13.7	Yes	Yes
Chronic Ulcers	12.1	Yes	No
Venous Ulcers	7.8	Yes	No
Traumatic Wounds	19.2	Often	Often
Amputation Wounds	1.7	Possibly	No

Figure 11. **(a)** Medicare.gov data highlight surgical and diabetic wound infections as the most common types. Figure created by the authors based on data from Nussbaum et al.[4] **(b)** Chronic wounds predominate in specialist care, with pressure ulcers, nonhealing surgical wounds, and DFU being the most common. Figure created by the authors based on data from Ashtikar et al. (2018).[139] DFU, diabetic foot ulcer.

Table 2. *Clinical trials of cold atmospheric plasma for chronic and acute wounds*

Study	*Wound Type*	*CAP Type*	*Sample Size*	*Treatment*	*Ref.*
Systematic review	Multiple cases	Multiple	N/A	Preclinical and clinical data synthesis	Gan et al., 2021[140]
5-year clinical follow-up	Healthy volunteers	APPJ	5	10–30 s, once or over 3 days; follow-up at 5 years	Rutkowski et al., 2020[141]
RCT on chronic VLU	Chronic	DBD	46	2 min/session, 1× or 2× per week for 12 weeks	Bakker et al., 2024[142]
Multicenter RCT versus best-practice dressings	Chronic	APPJ	78	30 s/cm^2 session, 3× week in 1st week, 2× week in 2nd week, then once a week	Strohal et al., 2022[143]
CAP safety against DFU	Chronic	DBD	20	1 min/session, once daily for 10 days	Lagrand et al., 2023[144]
CAP for chronic wound and skin regeneration	Chronic	DBD	48	2 min/session, 3× week for 4 weeks	Abu Rached et al., 2023[145]
Preclinical burn wound model	Acute	APPJ	12	45 s/session, multiple sessions up to 50 days	Oliver et al., 2023[146]
CAP improves microcirculation in acute wounds	Acute	DBD	20	90 s single session	Matzkeit et al., 2021[147]
CAP dressing aids healing of acute wound	Acute	DBD	10	2 min/day for 7 days	Van Welzen et al., 2021[148]

APPJ, atmospheric pressure plasma jet; CAP, cold atmospheric plasma; DFU, diabetic foot ulcer; DBD, dielectric barrier discharge; VLU, venous leg ulcer.

important. To address this need, Rutkowski et al. conducted a 5-year clinical follow-up of healthy volunteers who had previously received CAP (APPJ) treatment to control skin lesions. Their findings showed no malignancy, inflammation, or persistent adverse effects, and patient-reported outcomes confirmed sustained quality of life. The review by Gan et al. highlighted the therapeutic promise and skin compatibility of CAP, whereas the study by Rutkowski provided rare but critical clinical evidence supporting its safe long-term use.[141]

Subsequent randomized trials further confirmed the clinical promise of CAP in the treatment of chronic wounds. A 2024 study by Bakker et al. in RCT studies on VLUs showed that the cure rates of once- and twice-weekly CAP (DBD) applications were 53% and 62%, respectively, which were significantly higher than the 25% in the control group, supporting dose-dependent clinical effectiveness.[142]

These findings were further supported by Strohal et al. where a randomized, multicenter clinical trial was conducted comparing CAP (APPJ) treatment with best-practice wound dressings in 78 patients with chronic wounds of various etiologies. CAP treatment showed significantly accelerated granulation tissue formation, greater wound area reduction, and shorter time to complete healing. Infection control and pH normalization are also improved, eliminating the need for preservatives. There were no adverse events, and more than half of the patients found the treatment comfortable.[143]

Recent studies have also highlighted the antimicrobial potential of CAP. Lagrand et al. used daily CAP (DBD) application to effectively reduce bacteria.[144] In another study, Abu Rached et al. investigated the first regulatory-approved air-operated plasma plaster patch (DBD) in a randomized, multicenter clinical trial involving 47 patients with chronic wounds. An interim analysis report showed no serious adverse events in either the CAP or control group, supporting its safety for real-world use.[145]

Although most CAP research has focused on chronic wounds, emerging evidence supports its use in acute wound care. In a preclinical burn model performed by Oliver et al. CAP (APPJ) treatment effectively reduced bacteria without delaying wound healing, demonstrating safety even in inflamed, thermally damaged tissue.[146] In the study by Matzkeit et al., improved acute wound perfusion was observed after short-term CAP (DBD) application. Hyperspectral imaging revealed increases in deep tissue oxygen saturation, hemoglobin distribution, and tissue water distribution, supporting a role for CAP in enhancing early wound physiology.[147] In addition, Van Welzen et al. have shown that CAP (DBD) integrated wound dressings can improve tissue oxygenation, hemoglobin distribution, and hydration in donor site wounds, while reducing pain levels and being well tolerated.[148]

These findings suggest that CAP may be a valuable adjunct to acute wound care, particularly for pain control and improved tissue perfusion. Importantly, these recent studies challenge the conclusions of the systematic review, demonstrating that CAP can actively reduce pain and

inflammation without impairing healing in the acute setting, revealing a broader therapeutic potential beyond chronic wound applications.

Clinical evidence and device limitations. Although CE-marked CAP devices show good promise in clinical use, the quality of clinical data support has room for growth. Most trials were limited by small sample size, short duration, or lack of placebo control. Devices such as the kINPen MED and SteriPlas have demonstrated wound healing benefits, but their effectiveness in large, deep, or exuding wounds remains underexplored. Furthermore, cost, the need for specialized user training, and limited integration with existing wound care protocols continue to limit wider clinical use. Comparative studies with standard therapy are urgently needed to position CAP as a viable clinical alternative.

TAKE-HOME MESSAGES

- CAP delivers reactive species that enhance tissue repair and sterilization in chronic and acute wounds.
- Compared with traditional methods like NPWT, CAP enables shorter treatment times with less tissue trauma.
- Multiple CE-certified devices have demonstrated clinical efficacy and safety in Europe.
- CAP acts through physical rather than pharmacological means and is regulated as a Class IIb medical device under DIN SPEC 91315.
- While CAP shows promise, standardized treatment protocols and further clinical trials are still needed for broader adoption.

CONCLUSION AND OUTLOOK

Traditional wound care methods, such as negative pressure wound therapy for chronic wounds, can remove exudate, promote granulation tissue formation, and reduce the risk of infection, but they take time. Acute wounds can use special dressings to provide a moist environment, absorb fluids, and prevent contamination, but sometimes the cost-effectiveness depends on the situation. CAP offers an alternative physical approach that can enhance microcirculation and accelerate healing in chronic wounds; prevent infection and optimize the healing esthetics of acute wounds by reducing the risk of scarring. These advantages make plasma therapy uniquely versatile compared with conventional approaches. However, CAP has limitations, including the cost of the individual devices and accessibility to health care workers.

In recent years, with the development of minimally invasive technology in surgical and esthetic surgery, in addition to promoting wound healing, CAP is used to prevent wound healing complications and prevent and treat postoperative infections, and its contribution is expected. Clinical trials have shown that CAP has great potential in modern medicine and can be effective in treating various wounds without causing significant damage to healthy cells. However, CAP still needs to be used, and the treatment time must be precisely controlled according to the wound measurement (usually specified by the product according to the indication). The challenges of developing CAP equipment still exist, and it requires the input of specialized talents in different fields, such as techniques related to plasma generation, relevant regulations and production specifications, business development personnel, end users of wound care, and so on.

Plasma medicine is a transformative tool in modern health care, bridging basic research and clinical practice. Continued innovation and efforts to standardize treatments and address remaining challenges will be therefore critical to expanding its application and realizing its full potential in the wound care revolution.

AUTHOR DISCLOSURE AND GHOSTWRITING

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Abbreviations and Acronyms

3D = Three-Dimensional
AHL = Acyl-Homoserine Lactone
AK = actinic keratosis
APPJ = atmospheric pressure plasma jet
Ar = Argon
CAP = cold atmospheric plasma
CE = Conformité Européenne
CTGF = connective tissue growth factor
DBD = dielectric barrier discharge
DFU = diabetic foot ulcer
DIN SPEC = Deutsches Institut für Normung Specification
EMC = Electromagnetic Compatibility
EPS = extracellular polymeric substances
EU = European Union
FGF7 = fibroblast growth factor 7
H&E = Hematoxylin and Eosin stain
ICNIRP = International Commission on Non-Ionizing Radiation Protection
IEC = International Electrotechnical Commission
H_2O_2 = hydrogen peroxide
IRB = institutional review board
ISO = International Organization for Standardization

Keap1 = Kelch-like ECH-associated Protein 1
LDH = Lactate Dehydrogenase
MDR = Medical Device Regulation
MSE = Materials Science and Engineering
MTT/MTS = Tetrazolium-based cell viability assays
NCKU = National Cheng Kung University
N_2 = nitrogen
N/A = Not Applicable
NO = nitric oxide

NO_2 = nitrogen dioxide
NPWT = Negative Pressure Wound Therapy
Nrf2 = nuclear factor erythroid 2-related factor 2
O_2 = oxygen
OH = Hydroxyl radical
QMS = quality management system
RCT = Randomized Controlled Trial
RNS = reactive nitrogen species

RONS = reactive oxygen and nitrogen species
ROS = reactive oxygen species
RPS = reactive plasma species
SLM = Standard Liter per Minute
TGF-β = Transforming Growth Factor Beta
UV = ultraviolet
VEGF = vascular endothelial growth factor
VLU = venous leg ulcer