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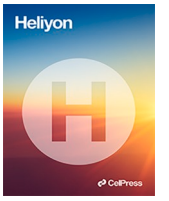

Applications of cold atmospheric plasma in immune-mediated inflammatory diseases via redox homeostasis: evidence and prospects

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ABSTRACT

As a representative technology in plasma medicine, cold atmospheric plasma (CAP) has beneficial outcomes in surface disinfection, wound repair, tissue regeneration, solid tumor therapy. Impact on immune response and inflammatory conditions was also observed in the process of CAP treatment. Relevant literatures were collected to assess efficacy and summarize possible mechanisms of the innovation. CAP mediates alteration in local immune microenvironment mainly through two ways. One is to down-regulate the expression level of several cytokines, impeding further conduction of immune or inflammatory signals. Intervening the functional phenotype of cells through different degree of oxidative stress is the other approach to manage the immune-mediated inflammatory disorders. A series of preclinical and clinical studies confirmed the therapeutic effect and side effects free of CAP. Moreover, several suggestions proposed in this manuscript might help to find directions for future investigation.

1. Introduction

Inflammation, a pathological process involving multiple cells and bioactive substances, is caused by various injurious factors, including pathogenic microbes, trauma, and abnormal immune responses [1]. The determination of whether inflammation is beneficial or harmful to the human body is challenging since it can both eliminate injurious factors and harm the body [2]. In most inflammatory diseases, inflammation effectively removes foreign bodies, leading to disease eradication. However, inflammation can persist and impede the healing process. Although drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoid, and cyclosporin A can effectively manage inflammation, the side effects observed in numerous clinical trials should not be overlooked [3–5]. The rapid development of plasma medicine may offer a potential solution to this problem.

Considered as the fourth state of matter, cold atmospheric plasma (CAP) is a unique gas containing abundant reactive oxygen species (ROS) and reactive nitrogen species (RNS), and can be generated by supplying sustained electrical energy at room temperature

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[6,7]. Additionally, high-energy particle interaction leads to the formation of radiation, heat, and electric fields. Plasma existed widely in nature before its discovery by humans. Through scientific and technological advancements, scientists have gained control over plasma generation and discovered its diverse applications in environmental, food and material fields, particularly in the field of biomedicine [8]. The variety of plasma generation devices and novel carriers of CAP active ingredients derived from dielectric barrier discharge (DBD) and atmospheric pressure plasma jet (APPJ) (Fig. 1) has facilitated patient application. The initial utilization of CAP in medicine stemmed from its antibacterial properties [9]. The therapeutic effects of CAP in oncology, dermatology, and dentistry have been demonstrated in recent years. These effects include the decrease of local microbial load, the remission of local inflammatory state, and induction of tumor cell apoptosis [10–12]. These factors suggest that that CAP can act as a primary or adjunctive treatment for diseases with few side effects, leading to optimal treatment outcomes. However, the mechanisms of CAP in modulating inflammatory responses in several immune-mediated inflammatory diseases at the cellular and more precise levels still need to be further investigated. It is necessary to make a stage summary on what we have known, for the progression of this field.

In this review, we summarize the mechanism and applications of CAP in several inflammatory diseases including chronic wound, inflammatory skin diseases, and autoimmune diseases. Safety and prospects of CAP treatment are also discussed to provide perceptions into the potential therapeutic applications of CAP in these diseases.

2. CAP intervention mechanisms in the inflammatory response

2.1. CAP alters the biological behavior of immune cells and cytokine secretion

The immune system plays a crucial role in protecting human against various injury factors. In short, it is composed of a series of immune cells and cytokines that devote to perform specific function respectively. Given that a few complete and readable overviews made by some excellent scholars, it is not necessary to reintroduce each of the component. The immense potential for the clinical use of CAP drives the research of its impact on cellular/molecular levels. Dysfunction of local immune microenvironment might be the pathogenic basis of immune-related diseases, regardless of autoimmune diseases or tumor immunity. Hence, it is of great importance to investigate the effect CAP made on immune cells and cytokines by *in vitro* studies and *in vivo* studies.

Bekeschus et al. comprehensively summarized the *in vitro* studies of the effect of CAP on different subpopulations of immune cells before 2018 [13]. Owing to the immunological function, neutrophils, macrophages and lymphocytes become the crucial focus for mechanism of CAP on immune system. In brief, neutrophils are closely associated with the wound healing process because of the dual role, removing microbes and necrotic tissue but exacerbating inflammation if excessive recruitment and retention happens in non-healing wounds [14]. Plasma treatment reduced metabolic activity in peripheral blood neutrophils, yet bactericidal activity and cell survival are unaffected [15]. More specifically, release of interleukin (IL)-8 was strongly increased and the formation of neutrophil extracellular traps (NETs) was also detected, which might be beneficial to microbial control. However, more evidence is required to

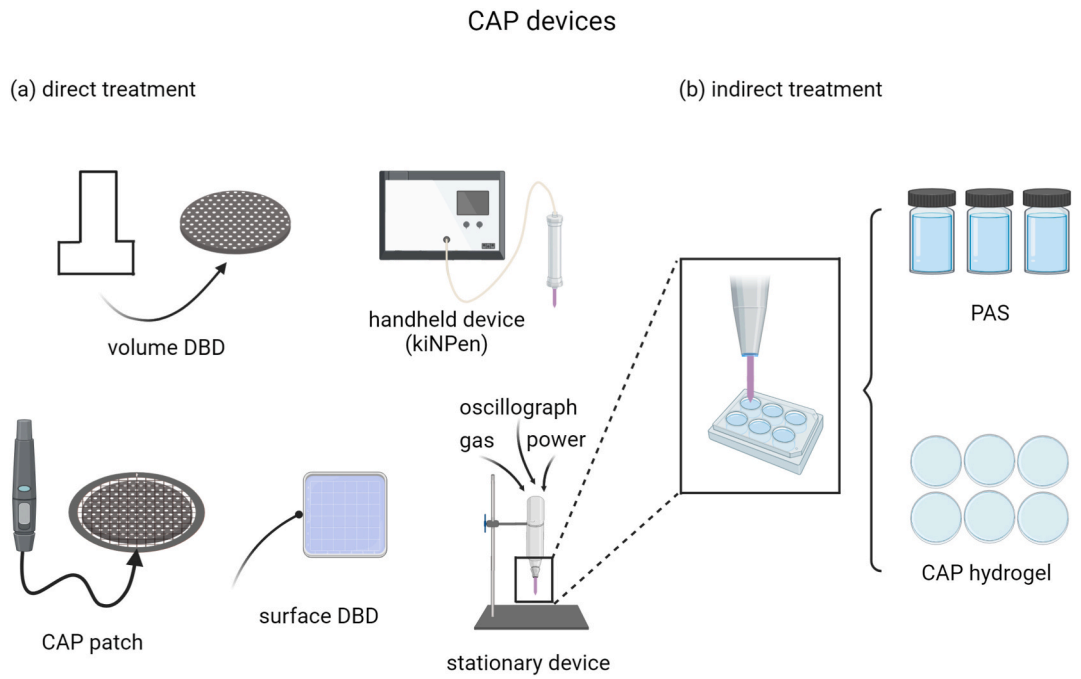

Fig. 1. Examples of CAP sources for directly or indirectly biomedical applications. (a) diagrammatic sketch of CAP generation devices discharged in a direct (dielectric barrier discharge, DBD) or indirect (atmospheric pressure plasma jet, APPJ) manner. (b) Plasma-activated solutions (PAS) AND CAP hydrogel made by PAS. Created with BioRender.com.

clarify whether NETs plays a positive or negative role in chronic wounds due to the opposite opinion [16].

Macrophages, derived from monocytes in general, participate in inflammation pathological process in several inflammatory conditions. For instance, macrophages drive the wound healing process through phenotypic changes among different stage after migration to the wound site [17,18]. Monocytes and macrophages seem to be well tolerated under CAP treatment, while some features might be changed after the process [19]. Exposure to DBD-derived plasma was shown to enhance the migration of macrophages, which might help reach the wound faster [20]. Besides, Zhang et al. demonstrated that the existence of ROS is vital to the differentiation of macrophage to M2 phenotype, which contribute to tissue repair and inflammatory suppression [21]. Furthermore, CAP treatment could promote the macrophage defense mechanisms to eradicate bacteria by increasing intracellular concentrations of ROS [22].

For lymphocytes, especially T lymphocytes, there are various subtypes distinguished by their surface marker, and each with a unique set of effector activities [23]. Compared with neutrophils and macrophages, lymphocytes, particularly in non-activated status, are quite fragile to exposure of CAP, which make it difficult to investigate changes in biological behavior [24]. However, alive cells still perform functions through redox regulating their cytokine secretion [13].

With regard to *in vivo* studies, various types of immune cells are involved in the immunological response to different inflammatory disorders, often accompanied by immune dysfunction. Th17 cells contribute to neutrophil infiltration and hyperproliferation of keratinocytes in psoriasis pathogenesis [25]. In the acute stage of eczema, Th2 cells mediate eosinophil infiltration, while Th1 cells (recruited by eosinophils and macrophages) dominate the immune response in the chronic stage [26]. In vitiligo, $CD8^+$ T cells play a particularly important role in destroying melanocytes [27]. However, the specific types and numbers of immune cells vary across disease stages and different diseases, making it challenging to identify a universal cell type involved in all types of inflammatory responses.

Although the therapeutic effect of CAP on various inflammatory diseases has not been widely studied, existing evidence suggests that CAP treatment or ROS directly modulates the functional phenotype of immune cells (Fig. 2). Kim et al. explored the role of ROS in psoriasis and found that imiquimod-induced psoriatic dermatitis could be regulated by enhancing the function of regulatory T cells [28]. In mice stimulated with imiquimod, Lee et al. demonstrated successful inhibition of Th17 cell differentiation [29]. *In vitro* experiments showed that plasma-treated medium suppressed the differentiation process from naïve $CD4^+$ T cells to Th17 cells. Moreover, it negatively regulated the activation of dendritic cells, resulting in inhibiting T cell activation. CAP treatment reduced the migration of

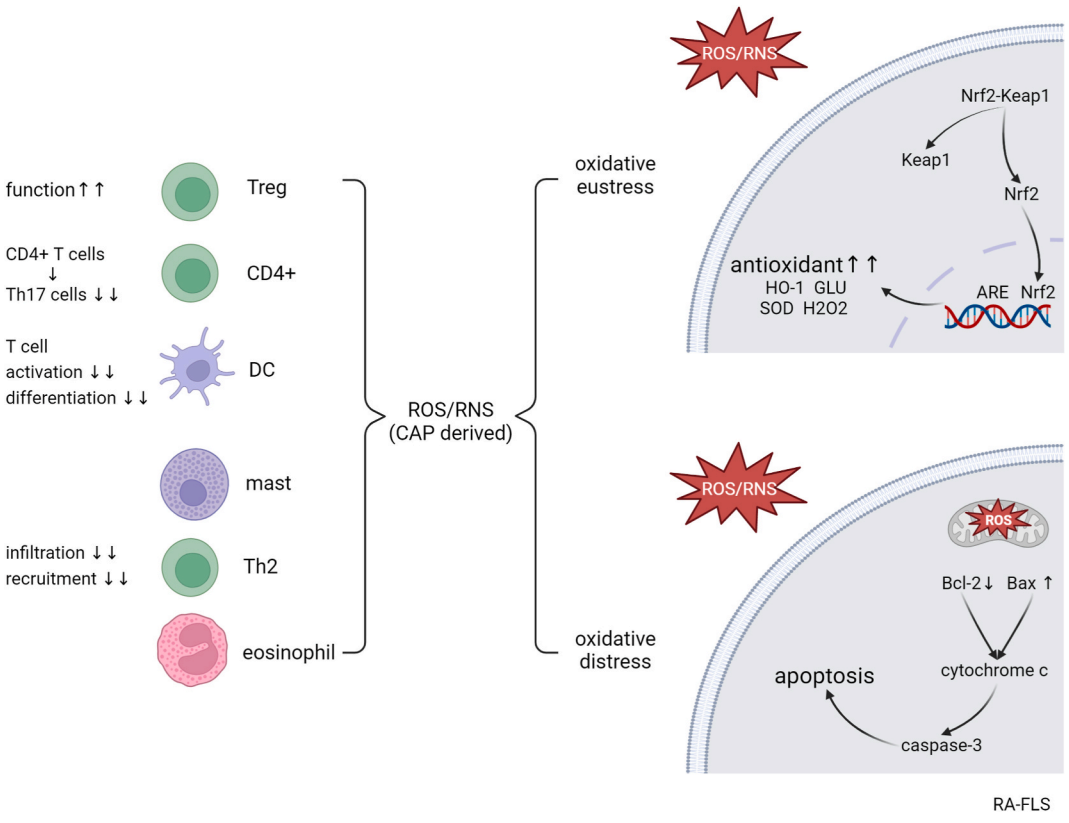

Fig. 2. Impact of CAP derived RONS on immune cells and oxidation-reduction system. It is proved that various immune cells (APC, various T cells, mast cell and eosinophils etc.) involved in pathogenesis of inflammatory diseases can be affected by CAP treatment, reflected in changes of cell functions and behaviors. Meanwhile, exogenous RONS decide the destiny in a dose-dependent way. Moderate oxidative stress (so called oxidative eustress) promotes the release of antioxidant substances and enhances cellular adaptability to various environments, while excessive oxidative distress (oxidative distress) induces cell apoptosis. Created with BioRender.com.

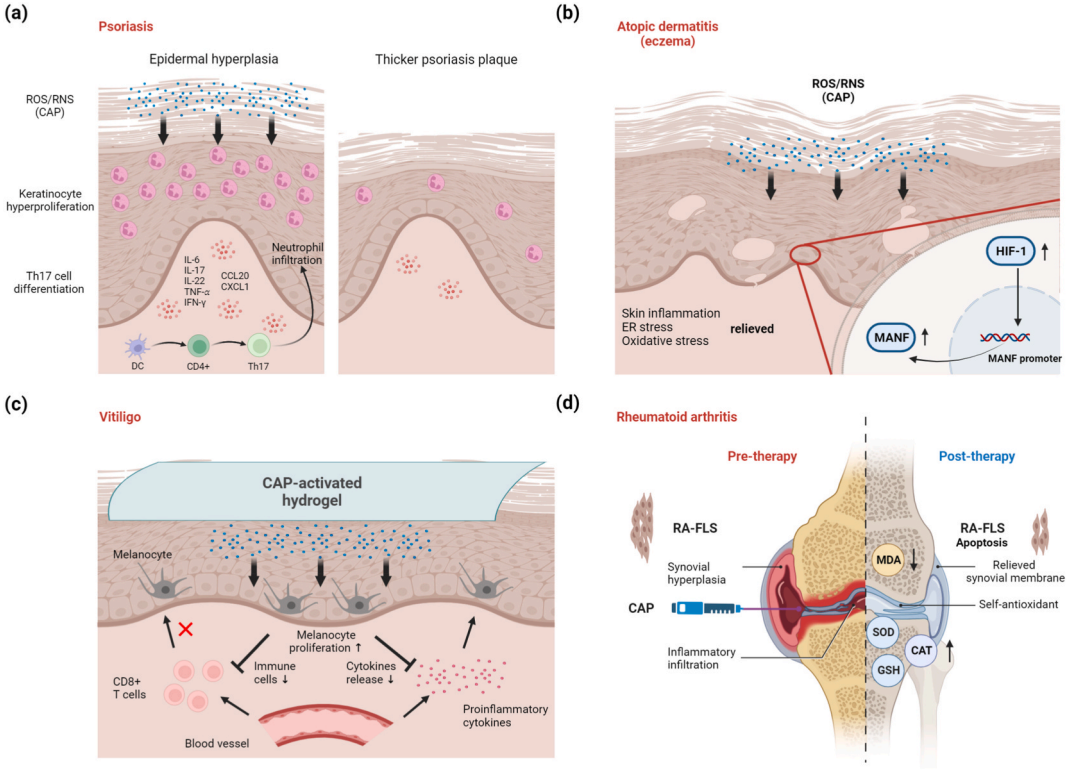

Fig. 3. CAP treatment alleviates inflammatory skin conditions and rheumatoid arthritis (RA). (a) CAP ameliorates psoriasiform dermatitis by reducing immune cell activation and differentiation, inhibiting over proliferation of keratinocytes and regulating secretion of cytokines and chemokines. (b) CAP treats atopic dermatitis (AD) by enhancing MANF mRNA transcription induced by hypoxia inducible factor-1 (HIF-1), showing decreased apoptosis in keratinocytes and relieved skin inflammation, ER stress and oxidative stress in lesions. (c) Therapeutic mechanism of CAP on vitiligo are revealed that RONS could protect melanocytes from targeting attack of $CD8^+$ T cells and inhibit the secretion of proinflammatory cytokines. (d) Arthropathy due to RA could be partly relieved by CAP treatment. RONS triggered antioxidant defense system as well as induced apoptosis in RA-FLS. Created with BioRender.com.

immune cells to the dermis, thereby inhibiting the development of eczema [30]. In a study on the mechanism of CAP irradiation in atopic dermatitis (AD), CAP-induced mesencephalic astrocyte-derived neurotrophic factor (MANF) expression promoted M2 macrophage differentiation, leading to changes in M1/M2 macrophage differentiation in tissue and blood. These findings, however, require further investigation [31]. Ma et al. confirmed the effect of CAP irradiation on macrophages, showing consistent high levels of M2-type macrophages, which promote tissue repair, during the healing process of radiation-induced skin injury [32]. Mice with vitiligo-like lesions were treated with CAP-activated hydrogel, showing low infiltration of immune cells ($CD3^+$ T cells, $CD8^+$ T cells, and dendritic cells) [33].

Intercellular communication involves the secretion of numerous known and unknown cytokines and chemokines by cells in the microenvironment of the affected area. These factors play a crucial role in physiological responses and can either contribute to healing or disease progression through intricate signal transduction pathways.

Leukocytes make changes in cytokine secretion in response to CAP expose *in vitro*. For neutrophils, a decrease in secretion of several inflammatory mediators (IL-1β, IL-6 and tumor necrosis factor (TNF)-α) was noticed after plasma treatment [13]. There was no notable change in the release of lymphocyte-secreted cytokines in resting peripheral blood mononuclear cells (PBMC), which include monocytes and lymphocytes. By comparison, IL-17 and granulocyte-macrophage colony-stimulating factor were significantly decreased in mitogen-activated lymphocytes [13].

Psoriasis pathogenesis is influenced by IL-6, IL-17, IL-22, TNF-α, interferon (IFN)-γ, chemokine (C–C motif) ligand 20 (CCL20), and chemokine (C-X-C motif) ligand 1 (CXCL1) [34]. Several studies have been conducted on CAP's anti-inflammatory properties. In an *in vitro* psoriasis model, where keratinocytes were co-treated with TNF-α and IFN-γ or treated with single lipopolysaccharide (LPS), CAP treatment inhibited gene expression related to IL-1β, IL-6, IL-8, TNF-α, IFN-γ, CCL17, and CCL22 [29,35]. Consistent findings were observed in *in vivo* experiments, with reduced expression of psoriasis-related cytokines and chemokines following CAP treatment. In an *in vitro* AD model, CCL11, CCL13, and CCL17, which recruit eosinophils, mast cells, and Th2 cells and cause inflammatory infiltration, were downregulated by CAP treatment [30]. Chronic inflammation in irradiated skin was effectively ameliorated by CAP, leading to alterations in cytokine content. Pro-inflammatory cytokines, such as IL-1β and TNF-α, were decreased, while the key wound healing cytokine IL-6 exhibited a temporary increase [32]. Furthermore, cytokines play a crucial role in essential processes of wound healing,

including angiogenesis, cell migration, and proliferation. Plasma treatment induces the release of various cytokines, such as transforming growth factors-β1/2 (TGF-β1/2) and fibroblast growth factor-2 (FGF-2), by stimulating gene expression, thus promoting the healing process [36,37]. Overall, numerous studies support the modulation of stimulated factors by CAP (Table 1).

2.2. Oxidative stress is a critical factor for CAP to determine cell fates

Redox reactions are fundamental to metabolic activities in living organisms, giving rise to various oxidants such as free radicals, ROS, and RNS [39]. The antioxidant defense system, which includes enzymes (superoxide dismutase, glutathione peroxidase, etc.) and molecules (glutathione, vitamin C, etc.) eliminates excess oxidants and keeps oxidants and antioxidants in balance. However, when the number of endogenous and exogenous oxidants surpasses the capacity of the antioxidant defense system, oxidative stress occurs, both in acute and chronic conditions [40].

An increasing body of evidence suggests a connection between oxidative stress and several chronic diseases, particularly inflammatory skin disorders [41–44]. It has been well established that ROS-mediated oxidative stress plays a role in dermatitis pathogenesis. Elevated levels of ROS may cause cell injury or death by interacting with nucleic acids, proteins, and polyunsaturated fatty acids on

Table 1
Changes of immune cells and cytokines after exposure of CAP.

Study	type of cells/ cytokines	Cellular/molecular level findings	Ref.
NETs formation in response to cold physical plasma	neutrophil	reduced metabolic activity less IL-8 secretion formation of NETs	[15]
Plasma stimulation of migration of macrophages	macrophage	migration of macrophages was enhanced	[20]
Cold atmospheric plasma promotes killing of Staphylococcus aureus by macrophages	macrophage	increased intracellular concentrations of ROS	[22]
ROS prevent psoriatic dermatitis through enhancing regulatory T cell function	Treg	hyperfunctional in elevated levels of ROS hypofunctional in lowered levels of ROS	[28]
CAP ameliorates psoriasis-like skin inflammation through inhibition of immune responses and up-regulation of PD-L1 expression	Th17 cell	differentiation was inhibited in the lymph nodes of the mouse model	[29]
	$CD4^+$ T cell	differentiation from naïve $CD4^+$ T cells to Th17 cells was suppressed	
	DC	negatively regulating DC activation	
Inhibition of inflammatory reactions in Nc/Nga atopic dermatitis mice by CAP	mast cell eosinophil	the numbers of mast cells and eosinophils reduced	[30]
Cold plasma irradiation attenuates atopic dermatitis via enhancing HIF-1α-induced MANF transcription expression	macrophage	M2 macrophage differentiation was promoted	[31]
Cold atmospheric plasma alleviates radiation-induced skin injury by suppressing inflammation and promoting repair	macrophage	the polarity of macrophages was changed to a repair-promoting phenotype	[32]
Successful treatment of vitiligo with cold atmospheric plasma-activated hydrogel	$CD3^+$ T cells $CD8^+$ T cells dendritic cells	less infiltration in vitiligo-like mice	[33]
Effects of cold physical plasma on human leukocytes	IL-1β IL-6 TNF-α	decrease in neutrophils	[13]
	IL-17 GM-CSF	decrease in mitogen-activated lymphocytes	
CAP-mediated anti-inflammatory therapy in psoriasis	IL-1β IL-6 IL-8 TNF-α IFN-γ CCL17 CCL22	inhibition of gene expressions	[34]
Inhibition of inflammatory reactions in 2,4-Dinitrochlorobenzene induced Nc/Nga atopic dermatitis mice by non-thermal plasma	CCL11 CCL13 CCL17	a significant decrease in the expression of all genes	[30]
Cold atmospheric plasma alleviates radiation-induced skin injury by suppressing inflammation and promoting repair	IL-1β TNF-α IL-6	expression of IL-1β, TNF-α was inhibited while IL-6 was temporarily increased	[32]
CAP induces angiogenesis through reactive oxygen species	TGF-β1/2 FGF-2	induction of gene expressions vital to healing process	[36, 37]
Inhibitory effects of CAP on inflammation and tumor-like feature of RA-FLS	NF-κB IL-6 RANKL MMP-3	the production of inflammatory factors and destructive factors was effectively reduced	[38]

Abbreviation: NETs: neutrophil extracellular traps; ROS: reactive oxygen species; Treg: regulatory T cell; DC: dendritic cell; CAP: cold atmospheric plasma; GM-CSF: Granulocyte-macrophage colony-stimulating factor; TNF-α: tumor necrosis factor alpha; RA-FLS: rheumatoid arthritis fibroblast-like synoviocytes; RANKL: receptor activator of nuclear factor kappa-B ligand; MMP-3: matrix metalloproteinases-3.

plasma membranes [45]. In the case of psoriasis, investigating whether oxidative stress-induced apoptosis can alleviate psoriatic lesions is crucial, as abnormal redox states have been observed in hyperproliferative keratinocytes [46].

Sies et al. proposed the theory of oxidative stress, classifying it into two categories based on oxidant exposure: "oxidative eustress" and "oxidative distress", representing low and high levels of stress, respectively [47]. Oxidative eustress enhances cellular adaptability to stress and new environments, while oxidative distress occurs when the intensity of oxidative stress surpasses beneficial levels. Therefore, it is hypothesized that CAP may influence the oxidative stress process by regulating ROS flux in tissues or cells (Fig. 2).

In particular, low doses of transient ROS are capable of activating the antioxidant system, such as by promoting the activation of the nuclear factor erythroid 2-related factor 2 (Nrf2)-antioxidant response elements (ARE) pathway and upregulating heme oxygenase 1 (HO-1) expression [48]. CAP treatment has been shown to increase Nrf2 expression and nuclear translocation, enhancing resistance to radiation-induced injury and DNA damage repair [32]. Studies on vitiligo and AD demonstrated elevated Nrf2 expression in CAP-treated mice [33]. Additionally, CAP treatment for AD resulted in a significant increase in HO-1 expression, an oxidative stress-related protein [31]. CAP has also been found to inhibit the progression of rheumatoid arthritis (RA) by attenuating antioxidant levels in tissues, thereby reducing excessive ROS consumption [49]. which contributed to consume excessive ROS. Conversely, transient but excessive oxidative stress mediated apoptosis in rheumatoid arthritis fibroblast-like synoviocytes (RA-FLS) through mitochondria membrane permeabilization [49], a crucial mechanism in oxidative stress-initiated apoptosis [50].

Inflammation and oxidative stress can mutually exacerbate each other. Initial oxidative stress can activate genes that encode pro-inflammatory cytokines, and subsequently activated immune cells release free radicals, highlighting a potential target for the treatment of inflammatory diseases [51].

3. Effects of CAP on immune-mediated inflammatory diseases

3.1. Chronic/non-healing wounds

The healing of skin wound is a complex process involving multiple physiological processes including tissue regeneration and scar formation, and following a breakage in the skin tissue caused by a damaging factor [52]. The healing process can be classified as acute and chronic wounds, depending on the time required for complete healing [53]. Current clinical treatments primarily involve surgical debridement supplemented by healing supportive measures such as dressings, antibacterial drugs, and growth factors [54,55]. Acute wounds such as abrasions, burns, and surgical incisions can follow the general process with normal and complete healing. However, chronic wounds such as vascular and diabetic ulcers often remain in the inflammatory stage for an extended time owing to the long-term presence of damaging factors and defects in local healing ability [56]. The wounds are often combined with bacterial infections [57], leading to delayed healing. Moreover, the frequent use of antibiotics contributes to the appearance of drug-resistant bacteria [58], and the presence of underlying diseases in patients further complicates the treatment outcomes. CAP has been extensively investigated by researchers worldwide, with numerous preclinical studies, clinical observations, and patient trials demonstrating its notable effects in stimulating wound healing.

The reduction of microbial load in infected wounds plays a vital role in eliminating delayed wound healing [59]. Therefore, the ability of CAP to promote healing in infected wounds by alleviating bacterial infection is highly appealing. Several studies have demonstrated the effectiveness of inactivating common microbes in clinical settings. For instance, a randomized, prospective controlled phase II study demonstrated a remarkable reduction in microbial burden in chronically infected wounds of 36 patients after 5-min treatment with argon-based cold atmospheric plasma [60]. Similar results were obtained in another randomized controlled trial using different plasma-generated equipment (the same equipment and the next-generation one) with a treatment duration of 2 min [61]. In a well-designed randomized clinical trial, Mirpour et al. reported powerful and immediate antiseptic efficiency of CAP, although the effect was temporary [62]. They also observed an accelerated healing process in diabetic foot ulcers [63]. The application of a portable, handheld plasma generator called PlasmaDerm showed safe and effective treatment of chronic venous leg ulcers, leading to significant reductions in bacterial load and wound size [64]. Additionally, numerous researchers have explored the use of CAP for eliminating bacteria resistant to multiple drugs in chronic wounds. Daeschlein et al. confirmed the efficiency of argon-based CAP in limiting colonization, a finding supported by several other clinical trials [65].

Although wound disinfection is a necessary condition for chronic wound treatment, the role of CAP in wound healing may exceed only disinfection. CAP therapy has already demonstrated its efficacy in promoting wound healing due to its anti-inflammatory effect, improved cutaneous microcirculation, and keratinocyte and fibroblast proliferation and migration in local chronic wound microenvironments. Stratmann et al. found no significant difference between the CAP and placebo groups in terms of decreased infection, which is inconsistent with the results of previous studies. However, they virtually observed that CAP contributes to wound surface area and time reduction for wound closure [66]. In a randomized clinical trial involving 44 patients with diabetic foot ulcers, proinflammatory cytokines secretion of IL-1, IL-8, IFN-γ, and TNF-α were significantly decreased after helium plasma jet application to the wound surface, indicating the latent capacity of decreasing inflammation for CAP [63]. Furthermore, Ma et al. investigated whether CAP could be an effective therapy for radiation-induced injury of skin tissues [32]. *In vivo* studies found that He gas based APPJ veritably ameliorated the morphology of injured tissues. Further research indicated that inflammatory infiltration in the radiation-induced immune microenvironment was improved due to changes in several cytokines' levels mentioned earlier, while cell proliferation, migration, and angiogenesis were promoted to accelerate wound repair. A study on CAP-induced proliferation of keratinocytes revealed that CAP treatment for 1–3 min can induce basal keratinocytes proliferation while long time exposure resulted in cell apoptosis [67]. Schmidt et al. examined the wound healing activity of the CAP jet using a series of cell and animal experiments. Both HaCaT keratinocytes and MRC5 fibroblasts were activated for migration and presented small gaps in scratch assays [68]. It was

assumed to relate to the downregulation of the gap junctional protein and several integrins which maintain adherent junctions and cytoskeletal dynamics. The CAP effect on keratinocyte activity was also certified by an earlier experiment, displaying that HaCaT keratinocytes expressed increased levels of β1-integrin and reduced levels of E-cadherin and epidermal growth factor receptor (EGFR) [69]. Liu et al. evaluated the relationship between the signaling pathway, NF-κB, and fibroblast proliferation. The results revealed that 15-s treatment of CAP to fibroblasts led to a significant increase in cell proliferation, EGF and TGF-βi secretion, intracellular ROS level, and the ratio of cells in the S phase, as well as expression of phosphorylated p65 and cyclinD1, but a notable decline in inhibitor kappa B (IκB) [70,71]. Furthermore, effect of CAP on increasing cutaneous microcirculation cannot be ignored. Increase of local superficial blood flow and number of capillaries can both contribute to the reconstruction of tissue microcirculation. Plasma-derived nitric oxide and heat energy are considered as the key factor, which further drive the transportation of nutrients and oxygen, facilitate the migration of immune cells and non-immune cells [72]. As for angiogenesis, a necessary process for wound healing. Arndt et al. observed that the expression of several wound angiogenesis relevant molecules in keratinocytes, fibroblasts, and endothelial cells were significantly upregulated after CAP exposure [73]. He et al. demonstrated that continuous CAP treatment for 2 weeks could promote angiogenesis of wound region in diabetes model mice [74]. The content of vascular endothelial growth factor (VEGF) and TGF-β in wound skin tissue were raised compared with the control group.

Although the therapeutic effect of CAP has been partly proven, the fundamental mechanism is still not well elucidated. According to the results of existing studies, CAP contributes to chronic wound healing at the cellular and molecular levels. At the cellular level, CAP mediates tissue reconstruction and repair, which is the result of activation, relocation, and proliferation of relevant cells (keratinocytes, fibroblasts, and vascular endothelial cells) due to the expression of a series of cytokines and growth factors triggered by ROS/RNS. The bacterial load and inflammatory response alteration also works and is worth further investigation (Table 2).

3.2. Inflammatory skin diseases

Inflammatory diseases affecting the skin are the most prevalent conditions encountered in dermatology. Despite the availability of various drug formulations and physical therapeutic strategies to alleviate the lesions, the occurrence of intolerable adverse reactions and inadequate response to therapy hinders the achievement of complete remission for these diseases [75]. Consequently, this negatively impacts the quality of the patient and imposes substantial financial burdens [25]. Inflammatory skin diseases can be categorized into two types: infectious diseases and non-infectious diseases, based on whether the disease itself is caused by an infectious agent. In this context, our focus primarily revolves around infectious skin diseases, which typically arise due to the presence of specific pathogens that can be targeted and eliminated through systemic or localized administration of antibiotic products. On the other hand, non-communicable inflammatory skin diseases commonly exhibit immune cell infiltration as a prominent feature within their pathological changes, suggesting a potential involvement of immune system dysfunction in their pathogenesis [76].

Psoriasis is a complex chronic inflammatory skin disease characterized by the presence of erythematous, thickened plaques covered with silvery scales. This condition arises due to abnormal keratinocyte proliferation and infiltration of immune cells [34,77]. While current treatment strategies can provide symptom relief, a definitive cure for psoriasis has yet to be discovered. Although great progress has been made in figuring out the pathogenesis of psoriasis, further efforts are required to identify potential targets for novel therapeutic approaches [78].

Several studies have explored the potential benefits of CAP in treating psoriasis. Gan et al. demonstrated the antiproliferative effects of CAP, which contribute to the resolution of psoriasiform-like skin lesions [46]. In a cell experiment, plasma-activated medium (PAM) was applied to HaCaT keratinocytes following preincubation with LPS/TNF-α. The results showed that PAM, abundant in reactive

Table 2
Researches of CAP applications on wound healing.

Wound type	Devices	object of study	Exposure manner	Main findings	Ref.
Chronic wounds	MicroPlaSter plasma torch	human (36)	daily 5-min treatment	a high reduction of bacterial load in treated wounds, regardless of the type of bacteria	[60]
	MicroPlaSter alpha and beta	human (24)	daily 2-min treatment	a significant reduction in bacterial load	[61]
Diabetic foot ulcers	APPJ (He)	human (44)	5 min 3 times a week for three consensus weeks	decreased bacterial load then accelerated wound healing	[63]
		human (45)	8 times	Reduction of wound surface and time to wound closure	[66]
Chronic venous leg ulcers	PlasmaDerm(®) VU-2010	human (14)	3 times per week for 8 weeks	bacterial load and wound size was significantly reduced	[64]
Heavily colonized wounds	Commercial argon assisted plasma	human (11)	unknown	MDR of all wounds reduced to a great extent	[65]
Dermal full-thickness ear wound	kINPen 11	mice	20 s daily for 2 weeks	a significantly accelerated wound re-epithelialization at day 3–9	[68]
Irradiated skin wound	APPJ	rat	30 s every other day until the skin wound healed	CAP ameliorated radiation-induced skin injury	[32]
Diabetic wounds	APPJ (He)	mice	90/180 s daily for 2 weeks	CAP obviously promoted diabetic wound healing	[74]

Abbreviation: APPJ: atmospheric pressure plasma jet; MDR: multidrug-resistant bacteria; PAM: plasma-activated medium; LTP: liquid type plasma; AD: atopic dermatitis; TEWL: transepidermal water loss; RA: rheumatoid arthritis; RA-FLS: rheumatoid arthritis fibroblast-like synoviocytes.

oxygen and nitrogen species (RONS), induced apoptosis in keratinocytes by increasing intracellular levels of ROS. Importantly, CAP was found to selectively target inflamed cells in localized lesions without causing harm to normal cells. Additionally, APPJ was applied in a psoriasiform dermatitis murine model, leading to improvements in epidermal hyperplasia within the lesions. The study also indicated a reduction in immune cell recruitment and pathological angiogenesis, further supporting the potential application of CAP in psoriasis treatment.

The anti-inflammatory effect of CAP has also been documented. Lee et al. demonstrated the positive impact of CAP on ameliorating psoriasis-like skin inflammation [29]. Following CAP treatment, they observed a significant inhibition in growth of epithelial cells, immune cell infiltration, and expression of cytokines and chemokines. Furthermore, CAP treatment was found to suppress Th17 cell differentiation and dendritic cell activation, both of which play crucial roles in psoriasis pathogenesis. High expression of programmed death-ligand 1 (PD-L1) in CAP-treated HaCaT cells was found to contribute to inhibit excessive T cell activation. Translational *in vitro* studies conducted at the cellular and molecular levels further support the notion that CAP treatment specifically targets keratinocyte hyperproliferation and T cell activation [79]. When HaCaT keratinocytes were exposed to plasma generated by a DBD device at an appropriate dose, apoptosis, disfunction of mitochondrion, and lysosomal leakage were observed. Furthermore, RONS induced the release of several psoriasis-related cytokines, including IL-6, IL-8, TNF-α, and VEGF. Notably, the levels of IL-12, which is positively correlated with T-cell activation and clinical features of psoriasis, consistently decreased as the plasma dose increased, thereby preventing further amplification of local skin inflammation. Although *in vivo* experiments were not conducted, CAP may have beneficial effects in treating psoriasis, based on these findings.

Kim et al. investigated whether a portable CAP patch could serve as a powerful therapeutic measure for inflammatory skin diseases and explored the inherent molecular mechanism [35]. Building upon previous research highlighting the role of calcium ions (Ca^{2+}) in psoriatic lesions, they demonstrated that opening calcium channels could alleviate psoriasis-associated characteristics by restoring abnormal keratinocyte differentiation and intercellular tight junctions. Importantly, they ruled out the possibility that the electric field generated concurrently with plasma contributed to these effects, further confirming the beneficial aspects of ROS/RNS and the potential application of CAP in inflammatory skin disorders.

AD, also named as “eczema”, is a chronic inflammatory skin disease influenced by a complex interplay of various factors, including genetic predisposition, environmental changes, and disfunction of the immune system of skin tissue [80]. The diagnosis of AD can be aided by its characteristic clinical features [81], which include: (1) a preference for childhood onset and persistent presence throughout life with little chance of complete cure; (2) the manifestation of recurrent, pruritic, localized eczema; and (3) frequent co-occurrence with other allergic diseases (allergic asthma, allergic rhinitis, etc.). The current clinical approach to AD treatment involves a combination of corticosteroids and systemic immunosuppression. However, the long-term use of these drugs carries the risk of adverse events that should not be overlooked [82]. Therefore, there is a need for high-efficiency, low-toxicity treatments for managing localized AD lesions. While there are few studies on the application of CAP in AD, emerging research suggests its potential.

Gao et al. studied the application of CAP in various types of superficial skin erosions, including pyoderma gangrenosum, traumatic wounds, and chronic eczema [83]. Seven patients with different types of skin lesions were recruited and treated with 5-min plasma jet irradiation every 2 days until wound healing was achieved. After several treatment sessions ranging from 2 to 8 times, all patients achieved complete response with no observed adverse effects. Particularly noteworthy is a clinical case of a 19-year-old patient with a three-month history of eczema, who experienced recovery after only two rounds of CAP irradiation. These findings demonstrate the potential value of CAP in treating superficial skin diseases, particularly eczema. However, further official clinical tests are needed to validate these results.

Another small-scale clinical study evaluated the therapeutic effect of CAP in AD, although further formal clinical trials are required [84]. Twenty-two patients with varying degrees of mild to moderate AD were randomly allocated to receive deal with MediPL Derm, an argon-derived indirect plasma generation equipment, or sham treatment. The study showed significant improvements in clinical severity and subjective symptoms without any safety concerns. Regarding the mechanism by which CAP alleviates dermatitis-like skin lesions, researchers suggest that it may promote the recovery of microbial diversity and reconstruction of the compromised skin barrier, thereby contributing to its therapeutic effects.

Vitiligo, an autoimmune disease characterized by abnormal inflammatory activation, presents as depigmentation patches resembling white spots [85]. Patients with vitiligo often experience significant psychological distress due to the lack of established therapeutic strategies for complete and relapse-free cure [86]. However, the pursuit of novel treatment approaches continues. Recently, an exciting study explored the use of CAP-activated hydrogel as a prospective strategy for ameliorating vitiligo lesions, offering hope to overcome this challenge [33]. The research group conducted a comprehensive investigation into the therapeutic effects of CAP on vitiligo, along with its potential molecular mechanisms.

In the initial pilot study, vitiligo-like mice and patients with active focal vitiligo were exposed to CAP (both APPJ and DBD), which demonstrated positive effects and served as the basis for subsequent studies. Further experiments revealed that both APPJ and CAP-activated hydrogel contributed to reduce depigmentation and redistribute follicular melanocytes in vitiligo-like lesions of mice. Building upon previous studies on the pathogenesis of vitiligo, the researchers delved into oxidative stress pathways, abnormal immune responses, and inflammation in detail. The results indicated that CAP effectively treats vitiligo by reducing immune cell infiltration, inhibiting the release of inflammatory and transcription factors, and enhancing antioxidant stress capacity. Moreover, compelling evidence from human trials supports the curative effect of CAP in patients in active stage of vitiligo. While further basic research and rigorous trials are required to validate the efficacy of CAP for other subtypes of vitiligo, we have ample reason to believe in its positive impact on this disease.

3.3. Autoimmune diseases

Autoimmune diseases arise from persistent and prolonged immune responses, where the immune system targets its own cells or molecules [87]. Various factors contribute to the development of these diseases, including genetics and environment [88]. Currently, our understanding of this group of diseases remains limited, and existing hypotheses do not fully elucidate the pathogenic pathways involved in autoimmune diseases. The mechanisms of immune damage differ among diseases, and individual variations among patients pose challenges in finding ideal therapies. Therapeutic strategies for autoimmune diseases primarily focus on two aspects: specific or non-specific blockade of immune response components involved in disease development and effective management of the pathological changes and tissue damage caused by the disease. Drugs like glucocorticoids, immunosuppressants, NSAIDs, and biological agents are used to delay disease progression by suppressing the inflammatory response. However, long-term use of such drugs may cause serious side effects [3,4]. Therefore, exploring means to suppress or ameliorate the local pathological changes caused by the disease could lead to new discoveries.

It is worth noting that the aforementioned inflammatory skin diseases can also be considered autoimmune diseases due to their association with autoimmunity. Although there have been relatively few studies on the use of CAP in treating autoimmune diseases beyond dermatosis, the lack of research in this area does not mean there are no remarkable discoveries waiting to be made. The application of CAP in treating RA can be considered a bold and innovative attempt. RA is a chronic autoimmune disease featured by persistent joint inflammation, damage of cartilage and bone, and excessive synovial tissue growth [38]. Despite significant efforts in this field, the exact pathophysiology of RA has not been fully understood. Evidence suggests that RA-FLS, which exhibit anti-apoptotic characteristics similar to tumor cells, play a crucial role in the progression of RA [89,90]. While medication-based treatments hold a prominent position, no viable strategy specifically targeting RA-FLS has been discovered [91]. The properties of CAP, such as its ability to induce apoptosis in tumor cells, have prompted studies exploring its application to suppress abnormal cell activation, including RA-FLS [6].

Several studies have investigated the effects of CAP on RA-FLS cells, revealing promising prospects for managing RA progression. Faramarzi et al. explored the effects of an argon-based CAP jet on cultured RA-FLS cells [38]. The treatment resulted in increased level of ROS, causing reduced cell viability and proliferation of RA-FLS cells along with an increased apoptotic ratio. Several inflammatory molecules, including NF-κB, IL-6, and MMP-3, were involved. Ding et al. demonstrated that a 120-s treatment of direct plasma significantly elevated intracellular ROS levels, reducing RA-FLS cell viability and altering the Bcl-2 to Bax ratio, molecular indicators of apoptosis [92]. Building upon these findings, the therapeutic effects of CAP on RA have been extensively investigated [49]. Results

Table 3
Researches of CAP applications on immune-mediated inflammatory diseases (w/o wound healing).

Disease	Devices	object of study	Exposure manner	Main findings	Ref.
Psoriasis	PAM	HaCaT cell		increase of intracellular ROS and keratinocyte apoptosis	[46]
	APPJ	mice	2 consecutive periods of 2 min separated by a 1 min pause, once daily	ameliorated morphological manifestation and reduced epidermal proliferation	
	LTP	HaCaT cell		high expression PD-L1 to suppress unwanted T cells' overactivation	[29]
	N_2-CAP	mice	60 s on day 3 and 4 after Psoriasis-likeskin inflammation was induced	inhibited increases in epithelial cell thickness and expression of pro-inflammatory molecules	
	CAP patch	HaCaT cell	5 min or 10 min	restoring abnormal keratinocyte differentiation and the collapse of the tight junction	[35]
		mice	5 min or 10 min for 7 consecutive days	lesions with psoriatic characteristics alleviated	
AD	APPJ	human	5 min, every other day	fully recovered after just 2 rounds of CAP irradiation	[83]
	MediPL Derm	human (22)	5 min, once a week for 3 weeks	eczema area and severity index score were significantly decreased	[84]
	Commercial APPJ device	mice	7 times, on Day 0, 4, 5, 7, 10, 11, 14, and 17 respectively	CAP decreases dermatitis severity, TEWL, and serum IgE level	[85]
Vitiligo	APPJ (He)	mice	1.5 min everyday, 1 month	CAP treatments reduced depigmentation, inflammatory cell infiltration in vitiligo-like mice	[33]
	CAP-activated hydrogel	mice	once every other day, 1 month	downregulated inflammatory factor expression	
	CAP-activated hydrogel	human (20)	2–28 weeks until at least one lesion partially recovered	partial repigmentation: 80 %; complete repigmentation: 20 % without hyperpigmentation in surrounding areas	
RA	APPJ (Ar)	RA-FLS (from RA patients)	30 s, 45 s, 60 s, 90 s, 120 s	CAP reduced cell viability, proliferation and promoted apoptosis in RA-FLS cells	[38]
	CAP-e	RA-FLS (purchased)	60 s, 120 s	suppressed viability, proliferation, invasion, and migration to surroundings with promoted apoptosis	[49]
	CAP-i	rat		inflammatory infiltration, synovial hyperplasia and angiogenesis were relieved by CAP with the proper dosage	

Abbreviation: APPJ: atmospheric pressure plasma jet; MDR: multidrug-resistant bacteria; PAM: plasma-activated medium; LTP: liquid type plasma; AD: atopic dermatitis; TEWL: transepidermal water loss; RA: rheumatoid arthritis; RA-FLS: rheumatoid arthritis fibroblast-like synoviocytes.

further indicated that CAP improves inflammatory infiltration and synovial hyperplasia by activating the antioxidant capacity of surrounding tissues. Simultaneously, CAP induces apoptosis of RA-FLS cells through mitochondrial apoptosis pathway, driven by the increase in spontaneously produced intracellular ROS (Table 3).

4. Safety

Before a new drug can be approved and used in patients, it must undergo rigorous clinical efficacy and biological safety evaluations. This requirement applies to CAP and CAP-derived active products as well. While immunomodulatory therapies like glucocorticoids and biological agents are commonly used in autoimmune and inflammatory diseases, they often come with various adverse effects [4]. However, numerous preclinical studies and clinical trials have shown that the novel strategy involving CAP is generally safe, with no observable adverse events, despite its capacity to induce cell death [93–96]. In fact, participants in these studies only reported a slight sensation of warmth [84] in the irritated area of the lesion, which is likely due to the heat generated by RONS produced by CAP.

To better understand the previous findings, the following viewpoints can provide clarity. First, the RONS generated by CAP, similar to drugs in tissues, do not persist for a long period. For instance, Choi et al. observed that the anti-inflammatory effect disappeared within 4 h in their *in vitro* model [30]. Moreover, cells under normal conditions are unlikely to be influenced by CAP treatment, as CAP does not induce apoptosis in keratinocytes [35]. However, Gan et al. demonstrated that cells in an inflamed state are more susceptible to CAP treatment [46]. CAP exacerbates the imbalance between the oxidation and antioxidant systems in inflamed cells, while normal cells can manage exogenous ROS and maintain balance.

Several studies have also monitored potential mutagenicity as a side effect [97–99]. Although no such toxicity has been detected in the aforementioned research, further preclinical studies are necessary. Long-term clinical trials are particularly crucial to further confirm the specific effects and potential risks of CAP treatment.

5. Prospects

In summary, CAP has demonstrated remarkable properties in alleviating several immune-mediated inflammatory diseases, including chronic non-healing wounds, psoriasis, AD, and RA (Fig. 3). CAP treatment modulates the activation, differentiation, and recruitment of various immune and non-immune cells, and it regulates the gene expression of multiple cytokines at the transcription and translation levels. Moreover, exposure to excessive exogenous ROS induces oxidative stress, which contributes to cell apoptosis induction or adaptation in a dose-dependent manner. Based on our findings, CAP contributes to the treatment of different immune-related diseases by employing partly similar mechanisms.

Although the clinical efficacy and biosafety of CAP have been extensively verified, further efforts are necessary to facilitate its translation into clinical application. It is crucial to thoroughly investigate the precise molecular mechanisms underlying the biological effects mediated by ROS and RNS in CAP. Additionally, establishing a standardized measurement protocol for the active ingredient in various plasma devices is imperative to facilitate result comparison among studies with diverse parameter settings. Furthermore, exploring alternative dosage forms of CAP, such as PAS and CAP-activated hydrogels, can improve patient acceptance and treatment convenience.

Most importantly, the potential relevance of CAP to other diseases involving similar immune response and inflammatory processes, as mentioned in this study, should be explored to broaden the scope of CAP applications in medicine.

Periodontitis is a common periodontal disease characterized by swollen and inflamed periodontal tissue. Long lasting inflammatory state leads to the destructive changes in periodontal tissue, which is the major reason for tooth loss in adult [100]. Although good habits for keeping oral hygiene and deep cleaning for teeth is recommended to control the symptoms, it cannot prevent the process of tissue destruction. Hence, how to reconstruct healthy periodontal tissue is an essential issue for periodontitis treatment [101]. Due to the similarity of inflammatory conditions in chronic wounds and periodontitis, it is possible for CAP to treat this chronic inflammatory disease by similar mechanisms (promote tissue reconstruction, reduce microbial load, fight inflammation, etc.) [102,103].

There is the possibility that chronic inflammation in gastric mucosa, can be relieved by CAP exposure. Chronic gastritis is divided into chronic non-atrophic gastritis and chronic atrophic gastritis based on histopathological assessment [104]. Infiltration of chronic inflammatory cells (plasma cells and lymphocytes primarily) without atrophic alteration in gastric mucosa is observed in chronic non-atrophic gastritis [105]. Studies has shown a clear correlation between gastric inflammation and oxidative stress [106]. Hence, it is worth investigating the potential efficacy in regulating inflammatory microenvironment and redox homeostasis in gastric mucosa.

Inflammatory bowel disease (IBD) is an immune-mediated inflammatory disease composed of ulcerative colitis and Crohn's disease. Despite of the unknown etiology, IBD is characterized by persistent inflammatory state colonic mucosa and immune imbalance mediated by multiple factors (genetic susceptibility, gut microbiome, etc.) [107]. To date, there are few effective strategies for the treatment of the disease, and the side effects brought by anti-inflammatory drugs and biological agents should not be ignored [108]. The unique feature of CAP in regulating inflammation intensity and promoting wound healing makes it a promising therapeutic strategy for IBD.

Data availability statement

No data was used for the research described in the article.

CRediT authorship contribution statement

Yuyi Ma: Investigation, Writing – original draft. **Tuanhe Sun:** Supervision, Writing – review & editing. **Kaijie Ren:** Writing – review & editing. **Tianhao Min:** Writing – review & editing. **Xin Xie:** Writing – review & editing. **Haonan Wang:** Writing – review & editing. **Guimin Xu:** Writing – review & editing. **Chengxue Dang:** Writing – review & editing. **Hao Zhang:** Conceptualization, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

List of abbreviations

APPJ	atmospheric pressure plasma jet
ARE	antioxidant response elements
CAP	cold atmospheric plasma
CCL20	chemokine (C–C motif) ligand 20
CXCL1	chemokine (C-X-C motif) ligand 1
DBD	dielectric barrier discharge
EGFR	epidermal growth factor receptor
FGF-2	fibroblast growth factor 2
HO-1	heme oxygenase 1
IBD	inflammatory bowel disease
IFN-γ	interferon gamma
IL	interleukin
IκB	inhibitor kappa B
LPS	lipopolysaccharide
MANF	mesencephalic astrocyte-derived neurotrophic factor
NETs	neutrophil extracellular traps
Nrf2	nuclear factor erythroid 2-related factor 2
NSAIDs	nonsteroidal anti-inflammatory drugs
PAM	plasma-activated medium
PBMC	peripheral blood mononuclear cells
PD-L1	programmed death-ligand 1
RA	rheumatoid arthritis
RA-FLS	rheumatoid arthritis fibroblast-like synoviocytes
RNS	reactive nitrogen species
ROS	reactive oxygen species
RONS	reactive oxygen and nitrogen species
TGF-β	transforming growth factors beta
TNF-α	tumor necrosis factor alpha
VEGF	vascular endothelial growth factor

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