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Protein Energy Malnutrition: Opportunities for Cold Plasma Technologies

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ABSTRACT

Protein energy malnutrition (PEM), a condition influenced by a complex interplay of biological and environmental factors, gut microbiota and low consumption of calories or protein, remains a serious global public health concern, especially in developing nations. Technologies based on cold atmospheric plasma (CAP), a mildly ionized gas rich in biochemically reactive species, have already demonstrated their strong potential as a simple, flexible and sustainable solution to many global challenges, from disease management to environmental remediation and food sustainability. This article explores the innovative strategies by which CAP technologies can address and mitigate PEM. Controlled preclinical studies indicate that CAP technologies can positively contribute to food security by enhancing protein availability and quality. By affecting oral and gut microbiota, CAP enhanced protein absorption. It can also modify the chemical structure of various food proteins to maximize their nutrient content and reduce allergenicity. This review addresses possible solutions using CAP in the mitigation of PEM and outlines key challenges and opportunities in translating CAP technologies into real-life solutions, particularly in regions where the burden of PEM is most significant.

1 | Introduction

Despite the significant advancements in medicine and health and in the food industry, protein energy malnutrition (PEM) remains a significant global health challenge, persistently affecting millions of individuals (Gómez-Velasco et al. 2023), especially in developing and underdeveloped countries (Khan and Ali 2023; Soni and Khan 2023; Zaheer et al. 2023). PEM is a multifaceted condition that can develop due to a severe deficiency in oral

intake of calorie- or protein-rich foods, nutrient malabsorption due to, for example, disease, or an energy expenditure that greatly exceeds the energy intake. Not surprisingly, it frequently emerges in conditions of poverty, food insecurity, and limited access to adequate nutrition, disproportionately afflicting vulnerable populations such as children, pregnant and lactating women, and the elderly (Fayemi et al. 2018). PEM compromises physical and cognitive development, weakens immune defenses, and increases susceptibility to life-threatening diseases (Hudson et al. 2000).

Karthika Prasad and Syamlal Sasi contributed equally to this study.

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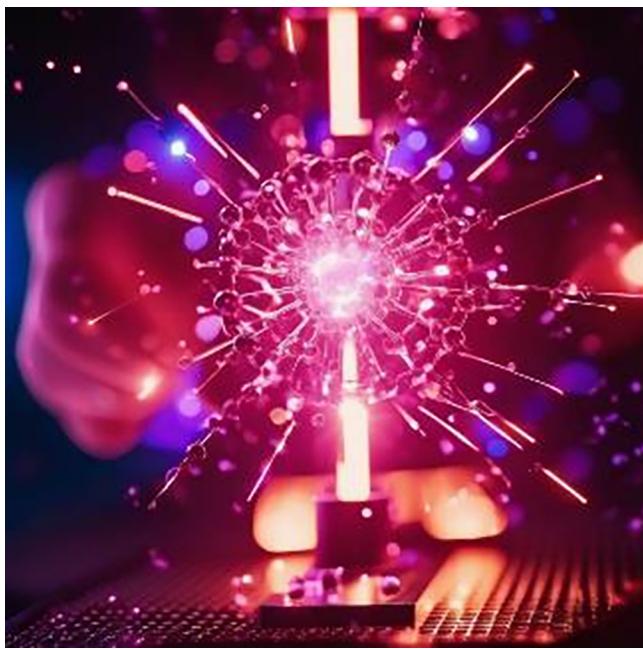


FIGURE 1 | How could plasma help combat the global protein malnutrition problem? As a highly reactive medium, cold atmospheric plasma can tackle multiple challenges that lead to PEM, by making the food safer, more nutritious and gut microbiome-friendly through the removal of disease-carrying microbes and pesticides, and modifying the chemistry and structure of complex molecules and breaking down antinutrients and allergens. In industrial biotechnology, it is also studied to improve the efficacy and selectivity of fermentation processes (Kabarkouhi et al. 2023), and may 1 day develop into a technology used for sustainable protein production, further improving food security in vulnerable regions. With continued research, plasma could play a vital role in future nutritional systems, making essential protein sources more accessible.

Even though the global age-standardized disability-adjusted life years (DALY) rates for PEM have declined since 1990, indicating long-term positive change, the absolute burden remains large. In 2022, an estimated 45 million children under five experienced medical wasting and the growth of further 148 million was stunted, leaving the health burden significant across all age groups and regions, both in developing and developed countries (WHO 2023; Zhang et al. 2022). Therefore, PEM mitigation remains a top societal priority, an urgent need for new innovative technology that can improve protein availability and enhance nutrient content and absorption, as well as food quality, is needed.

Cold atmospheric plasma (CAP) technologies are highly promising for addressing PEM (Figure 1). CAP is created using high-voltage electricity to induce partial ionization of a gas or a mixture of gases, creating a highly biochemically reactive cocktail of ions, free energetic electrons, potent oxidizers such as ozone, and radicals. As the gas is only partially ionized, its bulk temperature is close to room temperature (Chen et al. 2022; Khanikar and Bailung 2021), preventing heat damage and allowing its application in the food industry. It has successfully been used to treat fruit, seeds, vegetables, meat and dairy products, ensuring food safety and preservation. At the same time, its high biochemical reactivity makes CAP highly effective in inactivating a broad

range of pathogenic microorganisms, including bacteria, viruses, and fungi (Wang et al. 2016), (Koddy et al. 2021; Pan et al. 2019; Zhang et al. 2018), thus extending food shelf life even in environments where refrigeration and storage facilities are limited (Olatunde et al. 2019; Pan et al. 2019; Zhao et al. 2022). It can also effectively break down pesticides (Zhou et al. 2018) and alter the protein structure and amino acid profile of foods known to induce allergies, for example, roasted peanuts (Ji et al. 2020; Zhou et al. 2016), thus significantly contributing to improving protein bioavailability and digestibility, key factors in combating PEM.

PEM results from socioeconomic and environmental factors such as poverty, inadequate access to high-quality foods, poor sanitation and unsafe water, limited access to healthcare and other aspects. More recently, disturbances in gut microbiota have been increasingly recognized as one of the major factors in the onset of PEM and for the failure of some of the nutritional interferences to restore healthy growth (Subramanian et al. 2014), with several studies demonstrating persistent immaturity or dysbiosis of the gut microbiome in malnourished children that is not fully corrected by standard therapeutic foods, and microbiota-directed dietary interventions used as a proof-of-concept to show the impact of repairing microbiome composition on improving weight gain and recovery (Barratt et al. 2022; Iddrisu et al. 2021; Mostafa et al. 2024; Subramanian et al. 2014). These emerging discoveries on the relation between gut microbiota and nutrition provide another interesting avenue by which CAP-enabled technologies can mitigate PEM, by not only contributing to food security through its impact on, for example, agricultural productivity and food safety, but also on food chemistry, where it could be used to improve food digestibility, manage the levels of antinutrients and chemical and biological agents that could directly interfere with the health of human microbiome, thereby contributing to the broader multi-level strategies to improve protein availability, reduce infection and inflammation risk, and modulate microbiome-mediated nutrient metabolism.

To be an impactful tool in combatting PEM, CAP must be implemented as an integral element across the broader food and public health system, rather than as an ad hoc technological solution. In this review, we therefore focus on four targeted pathways for CAP to deliver nutritional impact: (1) reducing food allergenicity by chemically and structurally modifying antigenic epitopes to lower Immunoglobulin E (IgE) binding (with mandatory biochemical and immunological validation), (2) increasing protein bioavailability in plant and animal foods through controlled protein modification and degradation of antinutrients and other chemical and biological agents that may interfere with food digestion and maintenance of healthy gut microbiome, (3) improving productive efficiency by pre-treating feeds to enhance digestibility and thereby improve feed-conversion ratio (FCR) in aquaculture and livestock, and (4) safeguarding protein supply chains by extending food shelf-life and by providing alternative (conventional chemical-free) pathways to reduce infection risk.

2 | Understanding PEM

Clinically, PEM may manifest differently depending on its aetiology, chronicity, and physiological response. Classical categories

of severe PEM include: i) marasmus (i.e., the prolonged wasting secondary to prolonged energy and protein insufficiency, characterized by loss of muscle and subcutaneous fat), ii) kwashiorkor (a syndrome associated with protein starvation and oxidative/metabolic disarray, classically featuring bilateral pitting oedema, hypoalbuminemia, fatty liver, and dermatosis), and iii) marasmic-kwashiorkor (a hybrid featuring both wasting and oedema). When it comes to public health concerns, PEM is also described in terms of anthropometric phenotypes, such as wasting (low weight-for-height, a marker of acute undernutrition), stunting (low height-for-age, a marker of chronic undernutrition and developmental compromise) and being underweight (low weight-for-age, an index combining markers), each with different nutritional imbalance. These clinical conditions are the consequences of a multifactorial interaction between poor dietary intake, repeated infection (particularly enteric diseases), impaired nutrient absorption, and, more recently, changes in the gut microbiota that impair nutrient utilization and growth in response to standard therapeutic foods.

Treatment strategies for the PEM are tailored to address their different pathophysiological mechanisms and practical operational needs, with the use of, for example, ready-to-use therapeutic foods and infection control for acute wasting, and, for example, microbiota-directed dietary interventions for microbiota-associated impairments. This diversity and complexity in therapeutic needs is in part responsible for why many of the presently run programs succeed in reducing mortality but fail to fully re-establish long-term growth and development in the most vulnerable populations. This is a significant problem, given that tens of millions of under-fives are estimated to suffer from acute malnutrition at some point in their lifetime, with long-standing regional and socioeconomic differences in prevalence (Ashour et al. 2025; WHO 2023), and where wasting, stunting or being underweight as result of inadequate energy and protein intake and/or impaired utilization of nutrients remains a leading cause of morbidity and mortality among children worldwide.

Current public-health approaches to prevent and treat PEM are multilevel and include community-based management of acute malnutrition (CMAM) using ready-to-use therapeutic foods (RUTF) for severe cases, ready-to-use supplementary foods and targeted supplementary feeding for moderate malnutrition, micronutrient supplementation and food fortification programs, integrated WASH (water, sanitation, and hygiene) and infection-control measures, and broader food-security and social-protection policies. These measures reduce mortality, increase recovery rates and form the backbone of international nutrition programs (Ntaongo Alendi et al. 2025; Renzaho et al. 2025).

Despite the significant efforts from the global and local communities to address factors that lead to the development of PEM, operational and structural barriers (low coverage, supply and cost constraints, and unequal access) restrict the reach and sustainability of the interventions to the most vulnerable communities. Furthermore, the gap between the currently delivered standard therapeutic diet-based interventions and the best practices that are emerging from the growing mechanistic and clinical studies on the importance of addressing persistent immaturity or dysbiosis of gut microbiota in combating malnutrition also needs to be addressed. As such, future strategies on addressing PEM

should comprehensively address both the biological factors, including microbiome dysfunction, frequent enteric infections, and impaired utilization of nutrients, as well as socioeconomic determinants (e.g., poverty, food insecurity, inadequate sanitation and access to healthcare) to increase their long-term success (Leake 2014; Zoghi et al. 2024).

3 | Overview of CAP

A wide variety of CAP reactor designs exist; however, the technological set-ups used for food applications are often relatively simple, utilizing fundamental discharge principles for safe and effective surface treatment (Astorga et al. 2022). For example, an atmospheric pressure plasma jet (APPJ) system may consist of a DC/RF power supply operating within a frequency range of 10–100 kHz. Here, a flow of air (at a gas flow rate between 1–10 L/min) is used to push the plasma that is generated at the high voltage electrodes out towards the treated surface (typically places at a distance of 5–20 mm from the tip), and this system is well suited to the treatment of foods with a complex shape (Cullen 2022). Multiple jets can be organized into arrays for larger-scale processing. In another commonly used system based on the dielectric barrier discharge (DBD), the treated object is placed into the plasma that forms in the space between the electrodes (Holc et al. 2022; Holc et al. 2021; Recek et al. 2023). Such a system may be operated using either a DC or an AC power source with a voltage range of 40–100 kV, frequency range of 50 Hz to 50 kHz (for the AC), and a gas flow rate of 0–5 L/min.

In both types of systems, the contact between the food object and plasma-generated species induces the biochemical and physical processing the treated object. The outcome is dependent on the choice of the gas, the length and intensity of the treatment, and the chemistry of the reactive species. (Bárdos and Baránková 2010; Chen et al. 2022). When used for pathogen deactivation or pesticide decontamination, the interaction with plasma can damage the molecular structures and interfere with critical processes in the cell, leading to its deactivation and death (Kazemi et al. 2024). On the other hand, when used on seeds, the treatment can stimulate germination and improve seedling growth (Wang et al. 2017; Zhou et al. 2016). To achieve greater efficacies, CAP technologies can be readily combined with other, more traditional methods, such as a chemical or drug treatment or exposure to intense light (Zhou et al. 2019; Zhou et al. 2016).

Pesticide residues can be degraded with CAP across various chemical classes and food matrices. Table 1 summarizes several examples of CAP efficiency in breaking down different pesticide types and residue locations, providing general insights into their degradation kinetics and byproducts, as well as noting the challenges in the degradation of pesticide molecules located deeper within the food matrix.

Other types of systems, such as those generating spark, gliding arc, or microwave plasma, may offer other advantages. The key general features of frequently used systems in food safety, water remediation, biotechnology and medicine are summarized in Table 2 and Figure 2. Spark plasma, which is generated by electrical breakdown between two electrodes, may offer a higher energy density and a more localized treatment. It may, therefore, be

TABLE 1 | Degradation efficacy of CAP treatment by pesticide class and matrix type, noting degradation kinetics, and toxicity of thus-formed byproducts.

	Efficacy	Process and outcomes
Pesticide class		
Organophosphates	High	CAP effectively degraded diazinon, chlorpyrifos, acephate, malathion, and dimethoate. Degradation increased with higher voltage and shorter discharge gaps. Byproducts included less toxic phosphoric acid derivatives and alcohols as confirmed via FTIR and GC-MS (Lin et al. 2025).
Carbamates	Moderate to high	CAP degraded carbaryl, methiocarb, and aminocarb in water. Kinetics showed rapid dissipation within 1–5 min depending on voltage (70–90 kV). Hydroxylated and ring-opened derivatives as byproducts. Some intermediates may retain mild toxicity, requiring further treatment (Moutiq et al. 2020).
Pyrethroids	Lower, variable degradation	Limited reports in literature. These compounds are more stable due to their ester-linked aromatic structures. Degradation may require exposure longer than 1–5 min or at higher energy input > (80–90 kV).
Matrix type		
Surface residues	Effective	CAP excels at degrading residues on food preparation surfaces, fruit and vegetables (e.g., apples, cucumbers), and packaging materials. Surface oxidation and reactive species (O_3 , NO_x , OH^\bullet) drive degradation (Mousavi et al. 2017).
Internalized residues	Challenging	CAP has limited penetration depth. Internal residues in porous matrices (e.g., fruits, grains) may persist unless pre-treated or sliced. Efficacy depends on matrix porosity and treatment duration (Sojithamporn et al. 2023).

more efficient in the inactivation of microorganisms on surfaces while consuming very small amounts of gas (Khumsupan et al. 2023). Gliding arc plasma operates by moving an electrical arc along diverging electrodes and thus can cover larger surface areas while delivering both thermal and non-thermal effects (Dasan et al. 2017). In particular, this technology is suitable for the decontamination of bulk materials, like grains or large fruits and vegetables, while maintaining nutritional and sensory quality (Dasan et al. 2017; Khalili et al. 2018). The microwave plasma generates uniform and stable fields by ionizing gases with microwaves, eliminating contamination caused by electrode erosion. This consistent, non-thermal treatment is ideal for sterilizing food packaging or processing seeds while preserving their

nutritional integrity (Weihe et al. 2024). For these reasons, spark, gliding arc, and microwave plasmas are often considered more promising for scale-up, with a good level of treatment uniformity and control and versatility to suit a variety of applications (El Shaer et al. 2018; Ghezzar et al. 2008; Miao et al. 2023; Weihe et al. 2024).

3.1 | Plasma-activated Water

In addition to plasma being used as a dry treatment process, which is highly useful for extending the shelf life of powders and other foods with low levels of moisture, the chemical reactivity

TABLE 2 | CAP systems that are commonly used in food security and health applications.

Types of plasma	Generation mechanism	Operational conditions	Key applications	Safety notes	Food contact compatibility
APPJ	Gas flow directing plasma at atmospheric pressure	Atmospheric pressure, ambient temperature	Medical treatments, material processing, textile treatment	Ozone and NO_x: Significant generation; requires ventilation or scavenging systems. Electrode wear: Minimal if dielectric barrier used; metal shedding risk low. UV exposure: Moderate; shielding recommended for operators.	Compatible with most food-grade polymers (e.g., PET, PE, PP, PVC). May cause surface oxidation or etching on sensitive films (e.g., PLA, multilayer laminates).
DBD	Electrical discharge between electrodes with an insulating barrier	Atmospheric pressure, high voltage	Surface treatment, sterilization, ozone generation	Ozone and NO_x: High generation; active scavenging needed. Electrode erosion: Minimal due to dielectric protection. Uniformity: Can produce uneven treatment on complex surfaces.	Widely compatible with food contact materials. May cause surface oxidation on multilayer films or biopolymers.
Spark	High voltage converting gas into plasma	High voltage and atmospheric pressure	Food allergen mitigation	Ozone and NO_x: High levels; active monitoring and exhaust systems essential. Electrode erosion: High risk; metal particles may contaminate surface. Arc hazards: Requires insulation and spark containment.	Limited compatibility; risk of thermal damage or pitting on thin films. Suitable for robust surfaces (e.g., glass, stainless steel, thick polymers).
Gliding arc	Electric arc between diverging electrodes in fast gas flow	High voltage, gas flow	Environmental remediation, gas treatment, and agricultural applications	Ozone and NO_x: High; active exhaust required. Electrode erosion: Significant; metal contamination risk. Thermal effects: Local heating may affect sensitive matrices.	Limited compatibility with heat-sensitive food materials. Suitable for durable surfaces (e.g., glass, metal, thick polymers).
Microwave	Microwave radiation ionizing gas	Chemical processing, medical applications		Ozone and NO_x: Moderate; depends on feed gas and power. Electrode-free: No erosion risk; clean operation. EM interference: Shielding required to prevent leakage.	Excellent compatibility with most food contact materials. May induce crosslinking or discoloration in some biopolymers (e.g., gelatin films, cellulose).

PHYSICAL AND CHEMICAL EFFECTS, AND SCHEMES OF COLD ATMOSPHERIC PLASMA SOURCES

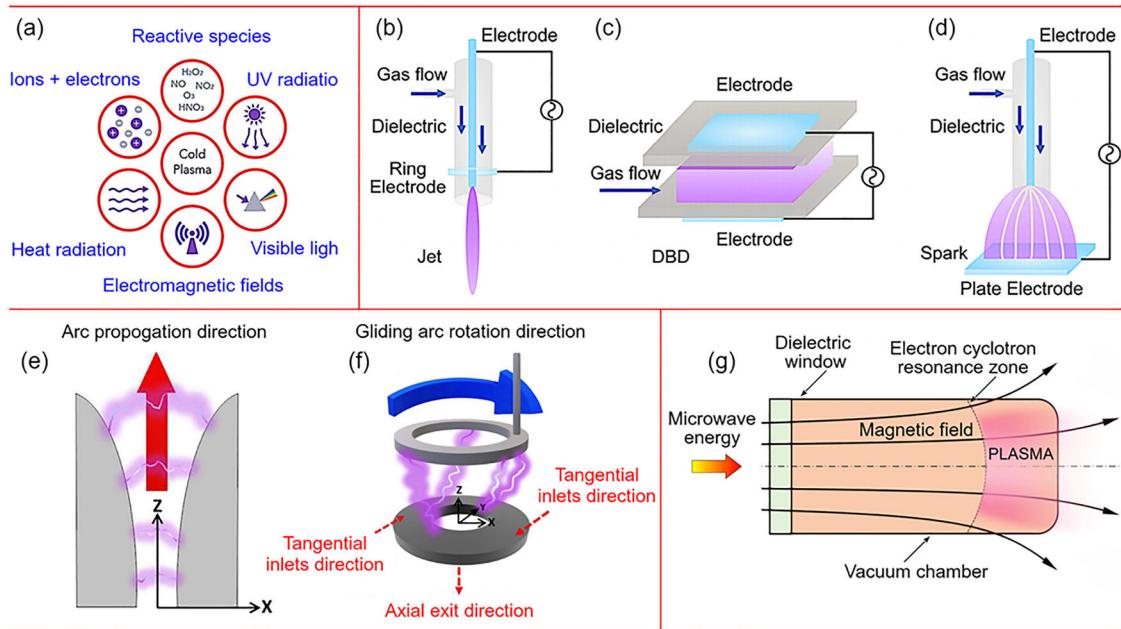


FIGURE 2 | Major constituents of cold plasma, with plasma generation mechanisms and various cold atmospheric plasma source configurations. (a) Physical and chemical effects generated by plasma (Lohan et al. 2024) and (b–g) several schematics of different cold atmospheric plasma sources. (b) Jet plasma, also known as atmospheric pressure plasma jet (APPJ), generates plasma at atmospheric pressure and uses a gas flow to direct the plasma jet towards a target. (c) Dielectric barrier discharge (DBD) plasma is created through an electrical discharge between two electrodes separated by an insulating barrier. (d) Spark occurs when enough voltage has been provided to convert some of the normally insulating gas into plasma. Reproduced with permission from Chen et al. (Chen et al. 2022). Copyright Elsevier, 2022. (e, f) Gliding arc plasma is generated between two diverging electrodes placed in a fast gas flow. Reproduced with permission from Mousavi et al. (Mousavi et al. 2019). Copyright Elsevier, 2019. (g) Microwave plasma is generated using microwave radiation to ionize gas, which produces plasma.

of gas plasmas can be transferred into a liquid medium, most commonly water, generating the so-called plasma-activated water (PAW) or plasma activated media (PAM) (Zhou et al. 2018; Zhou et al. 2020). PAW can then be used for spraying and soaking foods and seeds, or in place of normal water to stimulate the growth and productivity in agriculture and aquaculture systems (Dai et al. 2018; Dai et al. 2020). PAW was prepared using a dielectric barrier discharge (DBD) system with ambient air as the working gas. The exposure time was set to 10 min per 100 mL of water. Conductivity increased from 50 to 320 μ S/cm, and pH decreased from 6.8 to 3.2 following treatment. The activated water was stored at 4°C in sealed containers and used within 24 h to preserve its reactive properties. It should be noted that because the most basic plasma set-up can generate effective chemical cocktails on demand using only water, air and electricity (which may be obtained from a solar cell), at an ambient temperature and pressure, it is often considered an alternative to conventional chemical additives in both food safety and agriculture applications (Domonkos et al. 2021) as PAW may reduce chemical inputs. Also, PAW has been identified as one of the most energy-efficient methods for the delivery of CAP-based treatments. In one study, an underwater microbubble discharge was estimated to produce PAW at a cost of 0.01 euro per liter. In this work, only the cost of electricity was considered, with the microbubble discharge generated at 40 W for 15 min, resulting in an energy consumption of $E = 360$ J per 200 mL (Zhou et al. 2019). In comparison, the use of the corona discharge methods resulted in higher costs, reaching up to 0.27 euros per liter when corona discharge was operated in

the transient spark mode, with a power of 2.7 W for 30 min, corresponding to an energy consumption of $E = 4860$ J = 0.00135 kWh (Kučerová et al. 2021). It should be noted that the direct comparison between such technologies is difficult given the wide variability in the reactor design of the electric discharge systems employed, and other considerations, such as chemical composition and concentrations of active species generated. However, it provides evidence of the energy efficient nature of PAW, and its potential for integration into high-throughput systems.

Importantly, unused PAW over time loses its reactivity. The active composition and functional lifetime of PAW are species-specific and strongly dependent on pH, temperature, organic load, and container material. Shorter lived oxidants (e.g., O_3) typically have a half-life time of 20 min at 20°C (Steinhäuser et al. 2025), H_2O_2 typically shows half-lives on the order of hours (condition-dependent, roughly 1–24 h), while nitrite/nitrate species can persist for days to weeks when PAW is stored under cold, acidic conditions. PAW overtime revert back to plain water, and as such will not contribute to environmental pollution. With the strong interest in this technology, there has been significant progress in the development of commercially available systems capable of producing sufficient volumes of PAW to meet local needs, such as meat and dairy food processing.

This review explores how CAP technologies can provide a pathway mitigate PEM by improving food quality through enhancing

protein bioavailability and digestibility and supporting nutrient absorption. It explains how CAP can improve food security by reducing allergenic properties and extending the shelf life of foods by inactivating pathogenic microorganisms, thus preventing infections. The challenges, opportunities, and recent progress of these promising technologies, translated into the real world, are addressed, especially in regions where PEM is most prevalent.

4 | Application of Cold Atmospheric Plasma (CAP) in Addressing Protein-Energy Malnutrition (PEM)

While CAP has shown promise in various medical applications (Adnan et al. 2024; Bakhtiyari-Ramezani et al. 2024; Bhattacharjee et al. 2023; Koga-Ito et al. 2024; Liu et al. 2024), its potential to mitigate conditions that contribute to the development of protein-energy malnutrition (PEM) is yet to be explored. In this section, we will consider several pathways by which CAP can improve gut health, nutrient availability and absorption, reduce the allergenicity of protein sources, ensure food safety, mitigate the susceptibility of infections, and thus importantly contribute to improved public health outcomes. CAP generates a combination of short- and long-lived reactive species (referred to as reactive oxygen and nitrogen species, RONS), UV photons, charged particles, and localized electric fields at the plasma–liquid and plasma–solid interfaces, which are considered collectively responsible for inducing the observed biochemical changes in food matrices (Ahmed et al. 2025; Laroque et al. 2022; Sasi et al. 2025). These reactive species oxidatively modify protein side chains and (with controlled exposure) induce local backbone modification or unfolding that may result in enhanced protein solubility and accessibility to proteases. Numerous controlled experiments in model proteins and food models have reported enhanced in vitro proteolysis or altered digestibility of proteins after CAP treatment (Liu et al. 2025; Sruthi et al. 2022; Zhang et al. 2024). CAP has also been demonstrated to degrade or chemically alter antinutritional compounds (e.g., phytic acid, tannins, saponins) in grains and seeds under certain treatment regimens, and in doing so enhance the apparent protein bioavailability in treated food matrices (Arjmand et al. 2025; Charu et al. 2024; Kheto et al. 2023).

Simultaneously, CAP-generated RONS and secondary chemical species that are formed in the treated media as a result of plasma exposure (i.e., H_2O_2 , nitrite/nitrate derivatives, and low-molecular-weight oxidation products) can temporarily alter the behavior of microbial communities in water, in feed and on food surfaces, with initial findings showing changes in microbial communities relevant to amino-acid metabolism and short-chain fatty-acid pathways in treated systems (Cai et al. 2024; Lunder et al. 2025). Notably, these mechanistic impacts are extremely context dependent: plasma modality (e.g., DBD vs. APPJ), electrode geometry, feed gas composition, exposure time, food matrix composition, and post-treatment storage have all been shown to impact the resulting food chemistry and microbial response (Laroque et al. 2022; Yang et al. 2025). It is worth noting that while lab scale studies have provided an evidence-based mechanistic framework for the use of CAP in food processing, further translational studies are required to demonstrate the impact of CAP treatment on nutrition efficacy, and ultimately on protein

status of animal and human subjects. This transition requires further systematic chemical characterization of treated whole-food matrices, standardized in vitro digestion assays, parallel microbiome/metabolome analysis to establish effect sizes and safety, and ultimately clinical studies. And while the primary focus of this review is on the current demonstrated mechanistic evidence in support of the proposed avenues by which CAP can help mitigate PEM, it also explores the opportunities and translational pathways for CAP in nutrition (Figure 3), including in protein enhancement, antinutrient reduction, feed treatment, plasma-activated water, which may be useful to articulate outstanding research questions and guide future experimental designs.

4.1 | Targeting Gut Microbiota by CAP

Protein energy malnutrition is a result of inadequate protein and calorie intake and is often linked to compromised gut health and poor nutrient absorption. The causes of undernutrition extend beyond food scarcity or nutrient deficiencies, involving a complex interplay of biological and environmental factors (Diallo 2024; Headey and Venkat 2024; Raiten et al. 2024). Recent studies (Chang et al. 2024; Shennan et al. 2024; Zoghi et al. 2024) have highlighted the crucial role of the gut microbiome in this perspective. CAP has shown the potential to mitigate this issue by modulating gut microbiota. The gut microbiome is deeply involved in the metabolism of dietary components, influencing growth, development of the immune system, and overall health, especially in children during the first 3 years of life (Dogra et al. 2021; Yoo et al. 2024). The first 3 years of life represent a critical window for both the establishment and maturation of the gut microbiome and the development of the child (Laue et al. 2022). During this period, the microbiome plays a pivotal role in shaping health outcomes. Research indicates that interventions targeting the microbiome hold significant promise in combating undernutrition (Schröder et al. 2020). By leveraging the microbiome's potential, such interventions could improve nutrient absorption, immune function, and growth.

Gut microbiota are diverse, and there are not many studies exploring the potential of CAP to control microbial load in the gut. However, there is accumulating evidence indicating that the resident oral bacteria can translocate to the gastrointestinal tract through hematogenous and enteral routes, which may worsen various gastrointestinal diseases, including irritable bowel syndrome, inflammatory bowel disease, and colorectal cancer (Figure 4) (Kitamoto and Kamada, 2022; Kitamoto et al. 2020; Yamazaki and Kamada 2024). CAP has the potential to reduce pathogenic bacteria in the oral cavity (e.g., *Streptococcus* and *Staphylococcus* species), thus lowering the risk of translocation to the gastrointestinal tract and worsening malnutrition by disrupting the gut balance. While decreasing harmful microbial populations, favorable conditions for beneficial strain growth, like *Lactobacillus* and *Bifidobacterium*, are created. By improving the balance of beneficial microbes, CAP promotes a healthier gut environment and enhances nutrient absorption, which is one of the main issues in PEM.

Furthermore, CAP has been shown to affect the early stages of bacterial adhesion and promote decontamination of soft reline palatal obturators, highlighting the broad-spectrum antibacterial

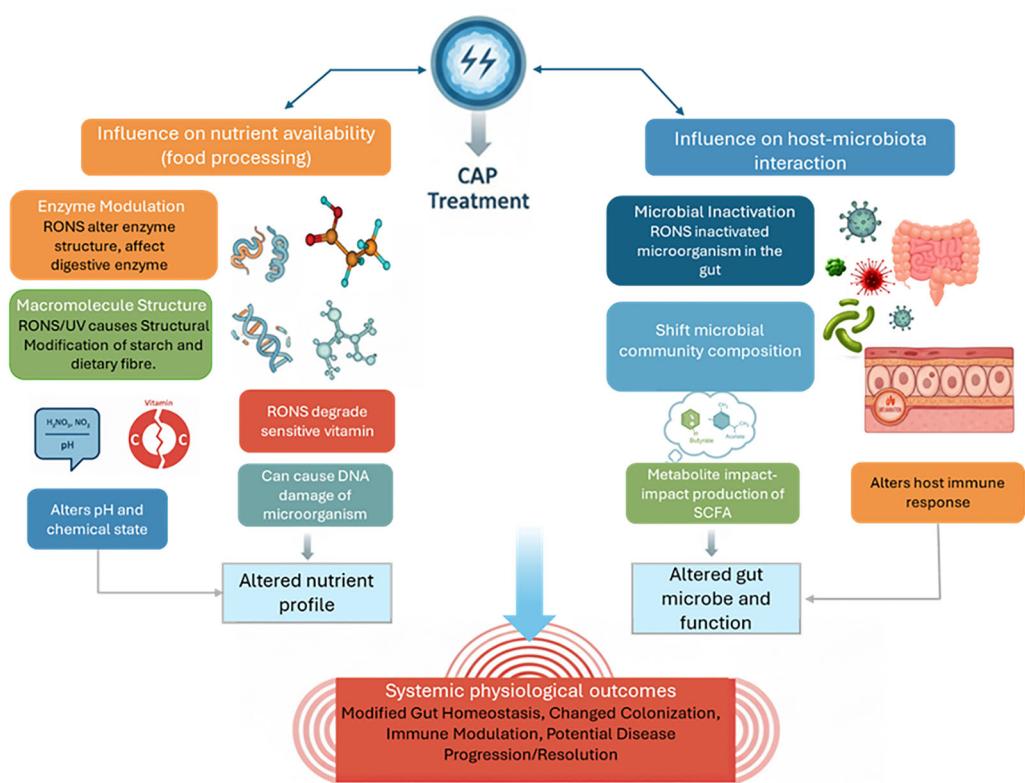


FIGURE 3 | Schematic representation of the mechanistic pathways by which CAP can affect food and the digestive system. CAP-generated RONS, UV, etc. can oxidize proteins, degrade antinutrients, and modulate gut microbiota, potentially improving nutritional properties of food post-harvest, and increasing amino-acid release and altering microbial metabolites in the gut.

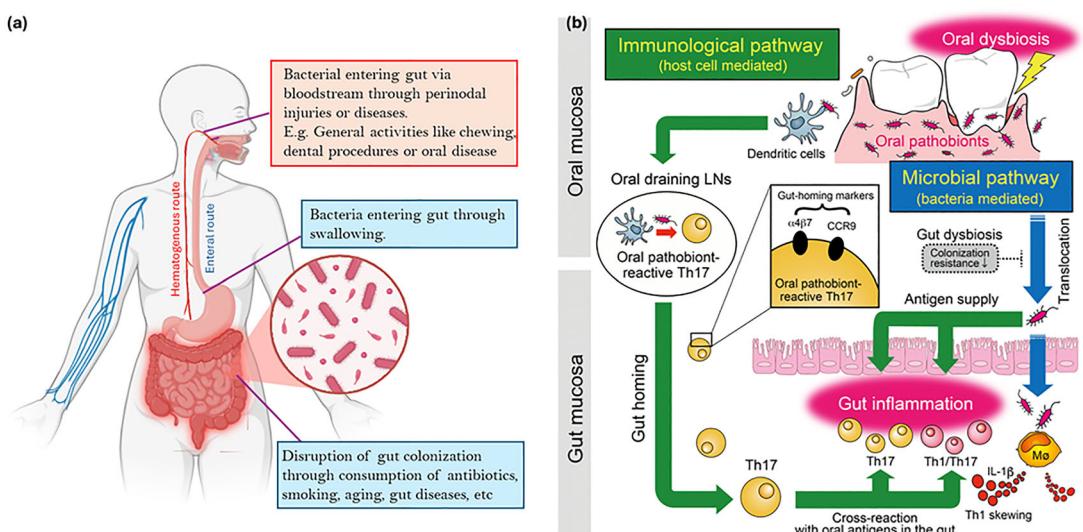


FIGURE 4 | Transmigration of bacteria from mouth to gut. (a) Possible routes of oral bacteria transmigration from the mouth to the gut. (b) Schematic representation of pathways contributing to gut inflammation driven by an oral pathobiont. Reproduced with permission from (Sho Kitamoto and Nobuhiko Kamada, 2022). Copyright Wiley, 2022.

potential of this family of technologies (Kim 2024). Studies have shown that a 60 s treatment with plasma jet using argon gas significantly decreased the microbial load of *Candida albicans* and *Staphylococcus aureus* found on a reconstituted oral epithelium (Delben et al. 2016). Similarly, treatment with a plasma jet has proven to effectively reduce a wide range of bacterial species in

the saliva, especially *Streptococcus mutans*, with treatment times ranging from 1 to 10 min per sample (Braný et al. 2020; Koban et al. 2011). Treatment with a plasma jet has also been shown to completely eliminate microbial infections in dental canals up to a depth of 1 mm with a 5-min daily treatment when using a mixture of argon and oxygen (Jiang et al. 2009), whereas other

studies have found that treatment with a plasma jet device using helium/oxygen gas can significantly reduce *Enterococcus faecalis* contamination in dental canals ex vivo. The above-mentioned study also claims that oxygen as a carrier gas was more effective than other gas mixtures, achieving substantial results within 2 to 8 min of treatment (Armand et al. 2019; Jiang et al. 2009). By targeting harmful bacteria and biofilms in the mouth, CAP can significantly reduce the risk of oral infections, inflammation, and periodontal diseases (Jungbauer et al. 2021).

Another way by which CAP helps improve gut bacteria is by enhancing the prebiotic properties of nutritional supplements like Spirulina. Prebiotics are selectively fermented food components that promote the growth of beneficial gut bacteria. By treating the supplements with CAP, the bioavailability of nutrients such as complex carbohydrates and amino acids is improved, which in turn supports the selective fermentation by probiotic strains like *Lacticaseibacillus reuteri* and *Lacticaseibacillus rhamnosus*, which are known to confer health benefits to the host (Pina-Pérez et al. 2024). During CAP treatment, the cell walls of Spirulina are effectively disrupted, making its nutrients more easily accessible to gut bacteria. In this manner, it controls pathogenic bacteria by facilitating the general health of gut microbiota further downstream by developing a more propitious environment for the growth and activity of beneficial microorganisms. Hence, CAP-treated nutrient powders can become a useful ingredient in functional foods and supplements to enhance gut health and general well-being (Pina-Pérez et al. 2024). Moreover, the synergistic role of CAP has been studied in conjunction with other therapies, such as plant secondary metabolites, to enhance its antimicrobial potency. This would create a much more holistic treatment approach toward gut health by utilizing each therapy for its strengths in such an application (Prasad et al. 2023). By leveraging these antimicrobial and probiotic-enhancing effects, CAP can be a promising adjunctive therapy to nutritional interventions aimed at treating PEM.

See Figure 5 for the study design schematic. It provides mechanistic insight into how CAP-treated interventions influence gut health and nutritional status, particularly in the context of protein-energy malnutrition (PEM).

4.2 | Improving Nutrient Availability via CAP

Protein-energy malnutrition (PEM) arises when protein and/or calorie intake is chronically insufficient to meet the body's physiological demands. Beyond dietary inadequacy, factors such as allergies and systemic inflammation can exacerbate PEM (Vassilopoulou et al. 2024). Over evolutionary time, juvenile undernutrition has driven adaptive responses in adult physiology aimed at conserving energy and protein. These include reductions in basal metabolic rate and lean body mass, particularly muscle protein, which comprises ~80% of total lean mass (Dulloo and Jacquet 1998). Such adaptations prioritize the preservation of vital organs and immune function, but they also diminish physical capacity and resilience.

While CAP cannot reverse these systemic physiological adaptations or address root causes of PEM, such as poverty, food insecurity, or limited access to protein-rich diets, it may offer

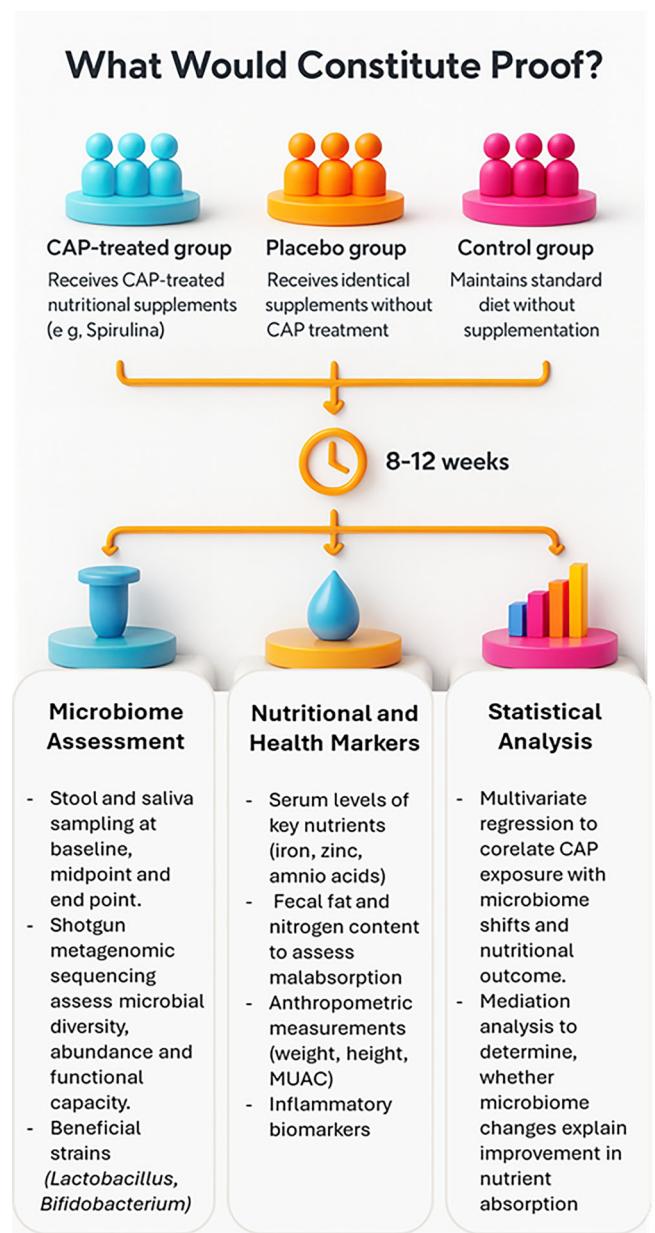


FIGURE 5 | Schematic overview of a randomized clinical trial design that may be used to evaluate the effect of CAP-treated nutritional supplements on human microbiome health and nutritional outcomes. The diagram outlines three intervention groups that receive either CAP-treated or placebo, and a control group, with sample collection at baseline, midpoint, and endpoint. Microbiome analysis includes metagenomic sequencing and quantification of beneficial strains. Nutritional outcomes are assessed via serum nutrient levels, fecal absorption markers, anthropometrics, and inflammatory biomarkers. Statistical analysis includes multivariate regression and mediation modeling to determine causal pathways.

targeted improvements in the quality, digestibility, and safety of available food sources. Specifically, CAP can enhance the functional properties of proteins, making them more bioavailable and palatable, and reduce their allergenicity—thereby expanding the usability of key protein sources for vulnerable populations.

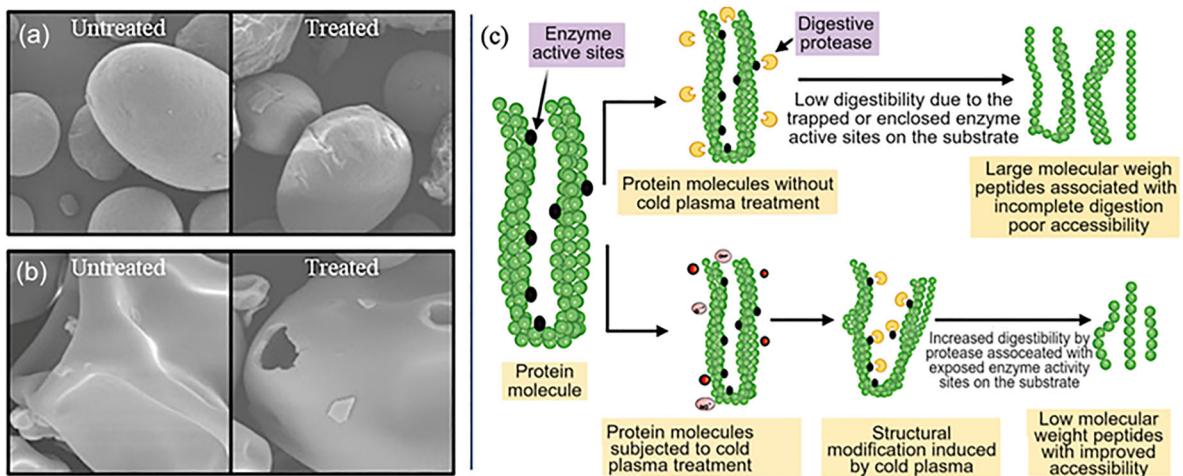


FIGURE 6 | Effects of CAP on protein structure and digestibility. (a, b) Scanning electron microscopy images (scale 20 μ m) showing surface topography of untreated and plasma-treated zein and soy protein isolate, respectively. CAP treatment induces morphological changes that enhance solubility and dispersibility. (c) Schematic representation of CAP-induced structural modifications that improve digestibility of plant proteins. These effects are limited to food-level enhancements and do not address systemic physiological adaptations associated with PEM. Reproduced from Li et al. (2024) and Olatunde et al. (2023) with permission. Copyright Wiley and Authors under respective licenses.

Recent studies show that CAP-treated protein powders exhibit improved solubility, dispersibility, and surface area, which can facilitate digestion and absorption (Basak and Annapure 2022). Unlike enzymatic hydrolysis, which often imparts bitterness, CAP treatment improves mixability and taste while preserving nutritional value. These effects are particularly beneficial for plant proteins like soy isolate, which traditionally suffer from poor solubility (Li et al. 2023). CAP also promotes gelation and alters rheological properties, improving texture and water-holding capacity (Zhang et al. 2021). Additionally, CAP can modify allergenic epitopes, reducing immune reactivity and enabling safer consumption of proteins like milk, soy, and peanuts (Olatunde et al. 2023; Ng et al. 2021). These mechanisms are summarized below.

CAP offers a promising technological adjunct to nutritional strategies aimed at mitigating PEM—not by altering systemic physiology, but by improving the digestibility, safety, and usability of protein sources, while enhancing the nutritional value of foods.

CAP improves the functional properties of proteins through various mechanisms, as shown in Figure 6 and summarized in Table 4. It increases protein solubility by adding hydrophilic groups to the protein surface, which prevents aggregation and enhances dispersibility (Basak and Annapure 2022; Mehr and Koocheki 2020). This is particularly beneficial for proteins like soy isolate, which traditionally have low solubility (Li et al. 2023). CAP also facilitates gelation by unfolding proteins and promoting fibrillar aggregate formation at lower temperatures, which improves the texture and water-holding capacity of gels (Zhang et al. 2021). Additionally, CAP alters the rheological properties of proteins, affecting viscosity and molecular weight distribution, and can reduce allergenicity by modifying allergenic epitopes (Olatunde et al. 2023).

These improvements in protein properties have a direct impact on managing PEM. By enhancing protein solubility and digestibility, CAP can ensure better absorption and utilization of amino acids,

which is crucial for individuals suffering from PEM who often face challenges in nutrient absorption. Higher bioavailability of proteins supports more efficient use of amino acids for essential functions such as tissue repair and immune response, helping to reduce protein deficits and support overall health. Improved protein bioavailability also aids in muscle synthesis and maintenance, addressing muscle wasting commonly seen in PEM. Moreover, CAP-treated proteins are easier to digest, reducing gastrointestinal distress and supporting better nutritional status. Improved protein bioavailability and digestibility lead to accelerated recovery, growth, and a reduction in symptoms of protein deficiencies, ultimately contributing to improved health and resilience against infections (Master and Macedo 2021).

4.3 | Reducing Allergenicity of Protein Sources by CAP

Food allergy is an exaggerated immune response that results in adverse health effects. It occurs when the immune system produces allergen-specific immunoglobulin E (IgE), which then interacts with allergenic proteins (Sharma et al. 2022; Verhoeckx et al. 2015). The allergens contained in various protein sources such as milk contribute to protein deficiencies for vulnerable groups such as children and individuals with weak immune systems. For this community, vital sources of protein and energy are completely eliminated from their diets altogether, thus resulting in an insufficient intake of essential nutrients—leading towards a lack of adequate growth and stunted development as well as a poor overall health status (Pudasainee and Anjum 2020). Furthermore, nutrient absorption and metabolism could be hindered by allergy-associated inflammation, with digestive issues further worsening malnutrition (Zubeldia-Varela et al. 2024). Hence, reducing food allergenicity is an important pathway for mitigating PEM and ensuring balanced nutrition among the concerned populations in both developing and developed regions.

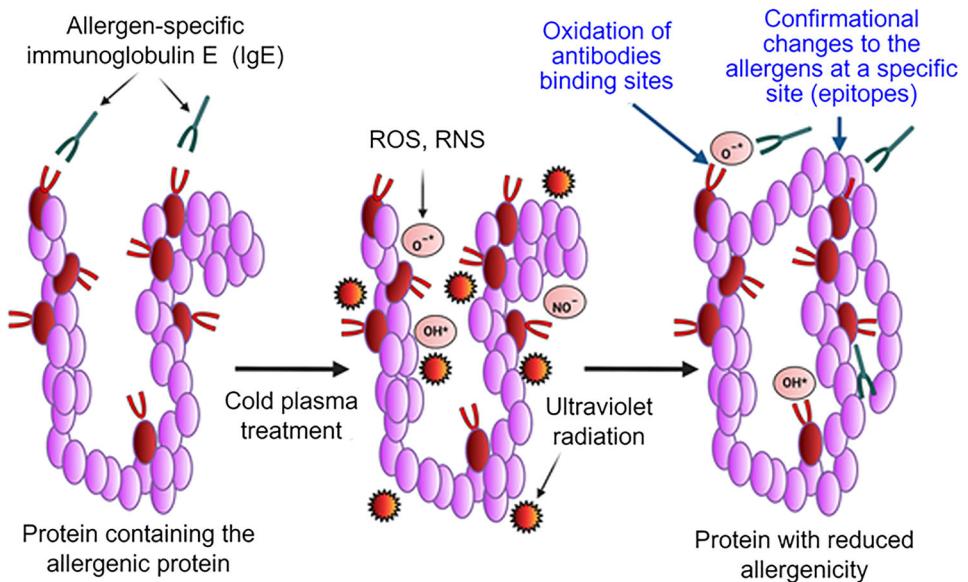


FIGURE 7 | Schematic representation of CAP reactive species interacting with the protein structures, leading to modifications that can reduce their allergenic potential. Reproduced with permission from (Olatunde et al. 2023). Copyright (2023) Wiley.

CAP holds immense potential in the reduction of protein allergenicity by efficiently modifying allergenic epitopes and reducing immune response, as shown in Figure 7 (Ng et al. 2021). This would be particularly significant for proteins associated with food allergies, such as peanuts and soy. Moreover, there have been several studies to understand if CAP has the capability to reduce the allergic effects of these products (Cheng et al. 2022; Venkataratnam et al. 2020; Zhang et al. 2021). With milk (Ng et al. 2021), it has been observed that CAP can lower the allergenicity of proteins through changes in their conformational structure and through the release of hydrophobic or hydrophilic residues that destroy or modify antigenic epitopes. However, with β -lactoglobulin, new epitopes that were formed during the treatment may enhance IgE binding ability. CAP reduces the levels of key amino acids found in antibody-binding sites, reducing the antigenicity of casein, α -lactalbumins, and β -lactoglobulin. CAP can also cause protein aggregation or fragmentation, which impacts both conformational and linear epitopes (Ng et al. 2021). This potential of CAP treatment for reducing the allergenicity of milk proteins with a minimal effect on the physicochemical properties of milk is promising for adding benefit to the dairy processing industry and potentially enabling a pathway to control PEM.

Similar studies have investigated the use of CAP treatment to reduce the allergenicity of nuts by altering antigen structures through interactions with free radicals and oxidation (Hsieh et al. 2023). The results demonstrated that CAP was effective in reducing the antigenicity of Ara h 1, a major allergen found in peanuts, by changing the protein's secondary structure (Venkataratnam et al. 2019). Similar is the case with most protein allergens studied thus far, where CAP treatment leads to oxidation, aggregation, crosslinking, and fragmentation of proteins associated with allergenicity (Gavahian and Khaneghah 2020), with several examples summarized in Table 3.

CAP treatment can alter both linear and conformational epitopes on allergens, thereby decreasing their ability to trigger allergic reactions. Studies have shown that CAP-induced changes, such as protein crosslinking, formation of insoluble aggregates, oxidation, and damage to antibody binding sites, contribute to reduced allergenicity by limiting IgE antibody recognition (Gavahian and Khaneghah 2020). It should be noted that some of the allergenicity studies reported in the CAP literature used indirect assessment to estimate the impact of CAP treatment on the target allergen, using structural and compositional changes to the protein structure rather than IgE binding to assess the outcomes of the treatment, as demonstrated in Table 4.

As such, while the initial findings indicate that CAP is effective in reducing allergens, future research is needed to better understand the impact of CAP processing on food allergenicity, quality, and nutrition, and the short- and long-term effects of thus-processed food on human health, particularly for individuals with food allergies. CAP can potentially be a valuable tool for improving food quality and mitigating PEM.

4.4 | Optimizing Amino Acid and Secondary Metabolites Production by Using CAP

Industrial microbial systems, such as yeast or bacteria, can be optimized using plasma technology to enhance amino acid production and thus enhance the nutritional content of fermented foods. It has been recently shown that plasma agitation can induce, by a single treatment, rapid and favorable phenotypic changes in *Saccharomyces cerevisiae* yeast. CAP induces a drastic increase in the capacity of the yeast to metabolize glucose into ethanol and improves the metabolic properties of the yeast (Recek et al. 2018). Minimal exposure to plasma treatment has been shown to alter the structure of the yeast cell membrane,

TABLE 3 | Effects of atmospheric and low-pressure (marked with *) plasma treatment on protein source of foods. t denotes CAP treatment time.

Protein Source	Plasma treatment conditions	Observations	Ref.
Almond	Plasma jet 17 V, 2.26 A, Ar $t = 5\text{--}20$ min	Reduced total microorganism count, no effect on color, peroxide value, or sensory qualities.	(Shirani et al. 2020)
Cashew	Glow discharge* 80 W, 50 kHz, syn-air $t = 0\text{--}34$ min	Reduced sucrose, increased anacardia acid and lipid extractability.	(Alves Filho et al. 2019)
Chia seeds	Plasma jet 1 kVA, Ar, $t = 30\text{--}120$ s	Increased viscosity, formation of aggregate structures, and improved stability of gel networks.	(Mutlu et al. 2023)
Chickpea	Glow discharge* 40–60 W, 13.56 MHz, 50 Pa $t = 10\text{--}20$ min	The decreased peleg rate is constant, and there is no effect on the peleg moisture constant.	(Pathan et al. 2023)
Flaxseed	Plasma jet over liquid 5 kV, 40 kHz, 750 W, air $t = 0\text{--}120$ s	Reduced solution pH and zeta potential, increased particle size. Protein carbonyls and lipid oxidation products first decreased and then increased with t .	(Nie et al. 2022)
Flaxseed	Plasma jet over liquid 5 kV, 40 kHz, 750 W, air $t = 0\text{--}240$ s	Decreased protein solubility, increased foaming, antioxidant, and emulsifying ($t = 5\text{--}15$ s). Increased surface hydrophobicity, mild protein oxidation.	(Yu et al. 2020)
Glycinin	DBD over liquid 40 kV, 12 kHz, air $t = 0\text{--}120$ s	Continuous and uniform gel network. Increased gel hardness, chewiness, and resilience. Improved gelling due to mild oxidation of $-\text{SH}$.	(Liu et al. 2022)
Glycinin	DBD over liquid 40 kV, 10–20 kHz, air $t = 2\text{--}5$ min	Reduced antigenicity due to modified amino acids in epitopes. Increased solubility and emulsification.	(Liu et al. 2021)
Grass pea protein	DBD 9.4–18.6 kV, air $t = 30\text{--}600$ s	Reduced intramolecular aggregation, increased water-air interface, and foamability at low temperatures. Increased aggregation, intermolecular β -sheets, conformation, and surface charge at long t .	(Mehr and Koocheki 2023)
Grass pea protein	DBD 9.4–18.6 kV, air $t = 30\text{--}60$ s	Lowest interfacial tensions at 9.4 kV, 60 s. Increased carbonyl groups, di-tyrosine cross-links, surface charge, and disulfide linkages with t and V .	(Mehr and Koocheki 2020)
Guar seed	DBD pin-to-plate (63 pins) 10–20 kV, 50 Hz, air $t = 5\text{--}20$ min	Increased structural and pasting quality at 10 kV. Reduced viscosity at 20 kV. Reduced anti-nutritional factors. Increased oxidation, polysaccharide, and protein destruction with t .	(Kheto et al. 2023)
Jackfruit	DBD Pin-to-plate 170–230 V, 59.94 Hz, 90 μS , air $t = 5\text{--}15$ min	Increased transition temperature, enthalpy, surface roughness, water solubility, absorption, swelling and retention, flowability. Decreased degree of crystallinity. Modulated components and protein secondary structure stability.	(Joy et al. 2022)
Mung bean	DBD, 80 kV RMS, 50 Hz, air $t = 10$ min	Improved gel firmness, 6 \times increased storage modulus, reduced minimum gelling concentration.	(Rahman and Lamsal 2023)

(Continues)

TABLE 3 | (Continued)

Protein Source	Plasma treatment conditions	Observations	Ref.
Mung bean	Plasma jet, 80–200 W, Ar $t = 1$ min	3× Increased production of γ -aminobutyric acid. Improved germination ratio, water absorption capacity.	(Chou et al. 2021)
Oat	DBD Pin-to-plate 170–230 V, 55.1 Hz, air $t = 15$ –30 min	Increased aggregation, reduced pH and zeta potential at 15 min. Increased protein unfolding, thiol group oxidation, free $-SH$ and disulfide content. Reduced surface tension, improved foaming.	(Eazhumalai et al. 2023)
Pea flour	Surface DBD 8.8 kV _{pp} , 3 kHz, air $t = 1$ –10 min	Increased water and fat binding capacities, protein solubility. Changes to the composition and structure of, for example, tryptophan.	(Bußler et al. 2015)
Pea protein isolate	DBD 9.4–18.6 kV, 20 kHz, air $t = 30$ –60 s	Increased carbonyl groups, di-tyrosine content, hydrophobicity, surface charge, polydispersity, α and β - β -structure, and creaming stability. Decreased free sulphydryl groups, ζ -potential, and interfacial tension. Loss of tertiary structure, globulin dissociation.	(Mehr and Koocheki 2020)
Pea protein	Plasma jet 20 kHz, 13.1 MHz, Ar 2D-DBD 10.3 W, Ar + 20% O ₂ ns pulsed 10 kV, 1 kHz, 4 mJ, air $t = 5$ –45 min	Changes in surface properties, aggregates, and β -sheet. Lowest impact on amino acid composition from 2D-DBD.	(Bu et al. 2023)
Pea protein	DBD + tartaric acid 100 W, 75 V, air $t = 0$ –20 min	Decreased particle size (at 10 min) and α -helix and β -sheet. Improved transparency, foamability, static stability, and protein fibrosis.	(Qu et al. 2023)
Pea protein concentrate	DBD 0–30 kV, 3.5 kHz, 0–1 A, duty cycle 70%, pulse width 10 μ s, air $t = 5 \times 2$ min	Improved gelling, mechanical strength, and solubility. Increased protein aggregation.	(Zhang et al. 2022)
Pea protein concentrate	DBD 0–30 kV, 3.5 kHz, 0–1 A, duty cycle 70%, pulse width 10 μ s, air $t = 5 \times 2$ min	Reduced fluorescence intensity. Enhanced gelling, protein unfolding.	(Zhang et al. 2021) (Zhang et al. 2021)
Peanut	DBD 35 V, 70 W, 2 A, air $t = 1$ –5 min	Increased solubility, exposed active amino groups, accelerated Maillard reaction, improved functional and structural properties.	(Yu et al. 2021)
Peanut flour (defatted)	DBD pin-to-plate (88 pins) 32 kV, 52 kHz, air $t = 15$ –60 min	Crosslinking, reduced immunoglobulin G binding capacity, decreased α -helices, and increased random coils.	(Venkataratnam et al. 2020)
Peanut protein	DBD AC 70 V, 1 A, air, $t = 1$ –4 min	Decreased hydrophobicity, free $-SH$ groups, and α -helix content with t . Increased β -sheets content, random coil.	(Ji et al. 2018)
Peanut protein	DBD 80 kV, 50 Hz, air $t = 0$ –60 min	Decrease α -helix content with t . Changes in turn, β -strands, and random coils.	(Venkataratnam et al. 2019)

(Continues)

TABLE 3 | (Continued)

Protein Source	Plasma treatment conditions	Observations	Ref.
Peanut protein	DBD pin-to-plate (88 pins) 32 kV, 52 kHz, air $t = 15\text{--}60$ min	Protein oxidation causing alterations in secondary structure. Reduced allergenicity of Ara h 1 and Ara h 2.	(Venkataratnam et al. 2020)
Peanut protein isolate	DBD 35 V, 0.2 A, air $t = 1\text{--}4$ min	Increased emulsion stability, turbiscan stability index, and free –SH content.	(Ji et al. 2020)
Peanut protein isolate	DBD 70 V, 1A, air $t = 1\text{--}10$ min	Non-linear changes in solubility, water holding capacity, total free –SH groups. Increased roughness, surface polarity, hydrophilicity, β sheets and random coils. Decreased α helices and β turns.	(Ji et al. 2019)
Peanut protein isolate	DBD AC 70 V, 1 A, air $t = 1\text{--}4$ min	Decreased pH, thermostability, hydrophobicity, α helices and β turns. Increased solubility, emulsion stability, water holding capacity, β sheets and random coils. No change in primary structures, protein fractions. Non-linear changes in micellar diameter in emulsions, total and exposed free –SH content.	(Ji et al. 2018)
Peanut protein isolate+dextran	DBD 35 V, 2 A, air $t = 0.5\text{--}3$ min	Rapid conjugation, breakdown of conarachin into small dextran conjugates. Decreased solubility, lysine and phenylalanine, thermostability, hydrophobicity, β sheets and random coils. Increased emulsion stability, α helices and β turns. No change in arginine, bathochromic shift.	(Ji et al. 2020)
Peanut protein isolate + lactose	DBD 90 W, air $t = 0\text{--}5$ min	Increased solubility, thermostability, α helix and β turns, surface etching. Non-linear changes in the degree of glycosylation. Decreased browning intensity, hydrophobicity, β sheets. Tryptophan and tyrosine are the sites for reaction. No effect on the formation of Amadori compounds.	(Yu et al. 2020)
Quinoa	DBD 50–60 kV, 37.2 kHz, air $t = 5\text{--}10$ min	Increased oil holding capacity for all samples. Changes in water holding capacity, protein and starch structure, additional starch-starch, starch-protein, or protein-protein intermolecular linkages.	(Zare et al. 2022)
Rice	DBD 20 kV, 50 Hz, air $t = 10\text{--}15$ min	Increased hydrophilicity, surface energy, protein. Reduced cooking time. Change in the bioavailability of iron improves binding between iron and protein.	(Akasapu et al. 2020)
Rice (Brown)	Glow discharge* 400 W, 130 Pa, He $t = 5$ min	Reduced phytic acid content, increased gamma-aminobutyric acid and γ -oryzanol in germinated rice.	(Li et al. 2023)
Rice (Chinese milled)	Glow discharge* 80–120 W, 13.56 MHz, 140 Pa, He $t = 20\text{--}120$ s	Decreased stability of protein network and reduced cooking time, no effect on quality.	(Liu et al. 2021)
Rice (de-oiled), corn bran	DBD or glow discharge* 50 Hz, 60 kV, 220–260 V, air $t = 5\text{--}30$ min	Increased extraction efficiency, antioxidant activity, in vitro digestion of polyphenols, maximum phenolic content at 260 V.	(Mehta et al. 2022)

(Continues)

TABLE 3 | (Continued)

Protein Source	Plasma treatment conditions	Observations	Ref.
Soybean glycinin	DBD 0–50 kV, 10–20 kHz, air $t = 2\text{--}5\text{ min}$	Oxidation of the peptide bond, and Trp, Tyr, and Phe amino acid residues. Changes in protein conformation, surface hydrophobicity.	(Liu et al. 2021)
Soy protein isolate	Surface DBD 9–11 kV, 3.0 kHz, air $t = 1\text{--}10\text{ min}$ Microwave (indirect) 2.45 GHz, 12 kW $t = 15\text{--}90\text{ min}$	Increased free amino acids/protein and protein-to-protein cross-links, changes in protein structure. No change in water content, pH for MW. Increased water content, decreased pH for DBD. Formation of insoluble aggregates. 89–100% reduction in major allergens β -conglycinin (Gly m5), glycinin (Gly m6).	(Meinlschmidt et al. 2016)
Soy protein isolate	DBD 40–60 kV, 80–100 Hz, air $t = 1\text{--}10\text{ min}$	No change in color. Decreased pH, ζ -potential, $-\text{SH}$, hydrophobicity, α -helices, allergenicity. Non-linear change in particle size. Increased carbonyl content, random coils, solubility, and emulsifying activity index. Oxidative loss of tryptophan.	(Zhang et al. 2021)
Soy protein isolate	DBD pin-to-plate 170–230 V, air $t = 5\text{--}15\text{ min}$	Enhanced techno-functional properties, aggregation, etching, and surface area. Altered β -turns and β -sheet.	(Dabade et al. 2023)
Soy protein isolate	DBD 50 kV, 75 Hz, $\text{O}_2\text{+N}_2\text{+CO}_2$, $\text{O}_2 = 20\text{--}60\%$ $t = 180\text{ s}$	Improved modification efficiency, solubility, water holding capacity, gelling, emulsifying, and foaming properties with O_2 .	(Li et al. 2023)
Soy protein isolate	DBD 16–20 kV, 50 kHz, 50 W, air $t = 0\text{--}15\text{ min}$	Increased intramolecular hydrogen bonding, free and reactive $-\text{SH}$, free carbonyl, unfolding of α -helices and protein aggregation. Maximum solubility, water holding capacity, foaming at 18 kV/ 15 min.	(Sharafodin and Soltanizadeh 2022)
Soy protein isolate	Plasma jet 18 W, 13.56–40.68 MHz, air $t = 0\text{--}250\text{ s}$	Changes in wetting, increased O_2 . Hydrophilization of soy powder delayed hydrophobic recovery by up to 1 month.	(Guo et al. 2018)
Wheat (hard/soft flour), intermediate wheatgrass	Glow discharge* 1 kW, 13.56 MHz, Ar+CO ₂ $t = 60\text{ min}$	Dehydration of flour, no change in protein content, solubility. Increased water absorption, solvent retention. Up to 6.7% damage to starch. Peak torque, aggregation changed differently based on flour type.	(Held et al. 2019)
Wheat germ	DBD 25 kV, air $t = 5\text{--}40\text{ min}$	Improved functional properties, foaming capacity, stability at basic pH, prevented oxidative spoilage at 5 min.	(Abargheli et al. 2023)
Wheat gliadin	Plasma jet over liquid 20 kV, 42 mA, 1 kHz, He+air $t = 0\text{--}10\text{ min}$	Improved water uptake ratio, foaming, electric conductivity, particle size, pH, hydrophobicity, and aromatic amino acids.	(Sun et al. 2021)
Wheat (whole grain and flour)	DBD 80 kV, 230 V, 50 Hz, air $t = 0\text{--}30\text{ min}$	No change in secondary structure. Increased flour hydration, pasting, final viscosity. Decreased endothermic enthalpy, crystallinity, starch depolymerization.	(Chaple et al. 2020)
Zein	DBD 40–60 V, 1.5 A, air $t = 2\text{ min}$	Reduced particle size. Increased conductivity, solubility, dispersion stability and encapsulation efficiency.	(Chen et al. 2020)

(Continues)

TABLE 3 | (Continued)

Protein Source	Plasma treatment conditions	Observations	Ref.
Zein	DBD 60–100 V, 1A, air $t = 70$ s	Hydrogen bonds broken in the protein secondary structure, loose protein conformation, more exposed sites to interact with water.	(Li et al. 2020)
Zein (in suspension)	DBD 50–125 V, 1 A, air $t = 0\text{--}5$ min	Decreased particle diameter, pH, viscosity. Increased electrical conductivity, free –SH groups, hydrophobicity, disulfide bonds.	(Dong et al. 2017)
Zein (powder)	DBD 75 V, air $t = 1\text{--}10$ min	Decreased particle diameter, pH, denaturation enthalpy. Non-linear response by –SH groups, solubility. Increased roughness. Irregular distortions and ruptures observed on the surface.	(Dong et al. 2017)

TABLE 4 | Allergenicity assessment of CAP-treated proteins noting the assessment type.

Protein source	CAP treatment conditions	Observations	Assessment type	Ref.
Glycinin	DBD over liquid 40 kV, 10–20 kHz, air $t = 2\text{--}5$ min	Reduced antigenicity due to modified amino acids in epitopes	Direct	Liu et al. 2021
Peanut protein	DBD pin-to-plate (88 pins) 32 kV, 52 kHz, air $t = 15\text{--}60$ min	Reduced allergenicity of Ara h 1 and Ara h 2	Direct	Venkataratnam et al. 2020
Soy protein isolate	Surface DBD + microwave	89–100% reduction in major allergens Gly m5 and Gly m6	Direct	Meinlschmidt et al. 2016
Soy protein isolate	DBD 40–60 kV, 80–100 Hz, air $t = 1\text{--}10$ min	Decreased allergenicity, oxidative loss of tryptophan	Indirect	Zhang et al. 2021
Peanut protein isolate + dextran	DBD 35 V, 2 A, air $t = 0.5\text{--}3$ min	Structural changes, no allergenicity data	Indirect	Ji et al. 2020
Almond	Plasma jet 17 V, 2.26 A, Ar $t = 5\text{--}20$ min	No effect on sensory qualities	Not assessed	Shirani et al. 2020

In the direct assessment, true allergenicity is measured using IgE binding and biological assays; in the indirect assessment, structural or compositional changes are used as proxies; references that made no mention of allergenicity or relevant proxies are marked as “not assessed”. t denotes CAP treatment time.

which in turn affects its metabolic activities (Figure 8). This treatment increases the activity of hexokinase 2 (Hxk2), an enzyme crucial for glucose metabolism, and boosts the production of secondary metabolites. The enhanced enzyme activity and metabolic output demonstrate how plasma treatment can significantly influence the efficiency of glucose utilization and ethanol production in yeast (Recek et al. 2018). Exposure of *Saccharomyces cerevisiae* cells to air-cold plasma increases cell membrane permeability and cytoplasmic calcium concentration and affects the level of cofactors ATP and NADH. These lead to changes in the metabolic processes of the yeast cells and could have implications for enhancing microbial productivity and bioconversion capabilities (Dong et al. 2017). Treatment with air cold plasma also increased the ethanol yield by 34% and the biomass of *S. cerevisiae* by 28%, which is attributed to the enhanced intracellular calcium concentration. A 75% decrease in extracellular ATP concentrations was observed in plasma-

treated yeast cells; conversely, extracellular NADH concentration increased fivefold. This is because of the accelerated glycolysis rate during alcoholic fermentation at low ATP levels. Changes in metabolic pathways after cold plasma treatment favor NADH production and makes air cold plasma promising technology for improving microbial fermentation processes and bioethanol production (Dong et al. 2021).

There are also other microbes that have shown increased metabolic activity and enhanced production of secondary metabolites after CAP treatment (Abarghuei et al. 2021; Ji et al. 2022; Lee et al. 2023; Prasad et al. 2023). In *Lactobacillus* species, which are widely used in fermentation processes for dairy products and probiotics, CAP treatment has enhanced the production of lactic acid by increasing the metabolic activity of these bacteria and thus optimizing the fermentation process (Niedzwiedz et al. 2020; Pina-Pérez et al. 2024). *Streptomyces*

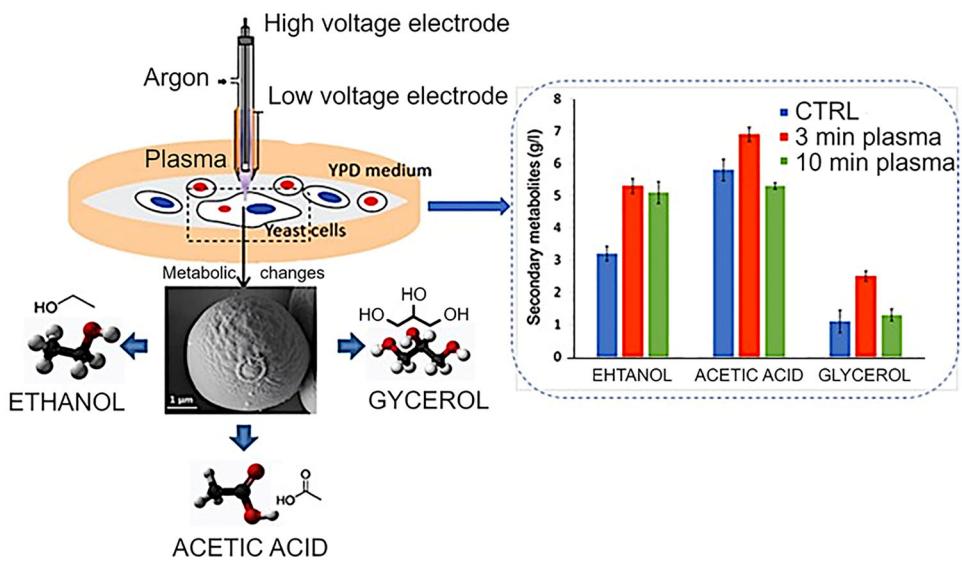


FIGURE 8 | Representation of plasma-induced changes on secondary metabolites of yeast. This study states that plasma can induce desirable metabolic changes in *S. cerevisiae* even after 3 min of treatment, which finally results in enhanced metabolic activity and more efficient conversion of glucose into ethanol with higher yields of secondary metabolites. Reproduced from (Recek et al. 2018) under the terms and conditions of the CC BY license. Copyright the Authors, 2018.

bacteria produce various bioactive compounds, including anti-cancer and antifungal agents. Metabolic stress induced from CAP treatment in these bacteria resulted in the production of secondary metabolites such as anthracyclines (anticancer drugs) and antibiotics (Murillo et al. 2023; Prasad et al. 2023); *Synechococcus* and other cyanobacteria produce biofuels like lipids and hydrogen gas. CAP might enhance the activity of enzymes involved in lipid biosynthesis, resulting in an increased yield of fatty acids that could be converted to biofuels. Secondary metabolites like pigments and vitamins may also be increased due to CAP treatment (Almarashi et al. 2020; Kongprawes et al. 2021; Priyanti et al. 2024; Yepez et al. 2022). Furthermore, *Bacillus* strains have also shown increased production of industrial enzymes like amylase and protease, which is crucial for industries like brewing, textiles, and food processing (Polsa et al. 2020; Tabar et al. 2022). Methanogenic archaea boosts methane production from organic matter, which is useful in wastewater treatment and bioenergy production (De Velasco-Maldonado et al. 2019). In certain cases, CAP may also reduce production of harmful secondary metabolites, that is, mycotoxins in *Aspergillus* species, by disrupting the fungal metabolic pathways (Ma and Jiao 2022; Wang et al. 2022; Zhao et al. 2023). It can also disrupt biofilm formation in pathogenic bacteria like *Pseudomonas aeruginosa*, by damaging the bacterial cell walls and inhibiting quorum sensing (the process by which bacteria communicate) (Brun et al. 2018; Zhang et al. 2023; Ziuzina et al. 2015). CAP-enhanced microorganisms could be developed as dietary supplements or added to staple foods to fortify them with essential amino acids, combating protein deficiency.

Recent research shows that CAP treatment can significantly impact the phytochemical properties and bioactive content in plant seeds, such as oats (Lee et al. 2023). Plasma generated with a surface dielectric barrier discharge (SDBD) is able to increase the content of bioactive phytochemicals present within oat sprouts during the germination process. During germination,

CAP treatment has been shown to stimulate the production and accumulation of a range of bioactive phytochemicals within oat sprouts. These include essential compounds such as antioxidants, vitamins, and secondary metabolites crucial for plant growth and development, as well as their nutritional and health benefits. The enhanced content of these bioactive substances can lead to improved physiological activities and overall plant health and importantly, contribute to the mitigation of PEM (Sera et al. 2010; Sheteiwy et al. 2019), especially in regions where plant-based proteins are the primary source of nutrition.

4.5 | Mitigation of Infections in Humans Affected by PEM

The response of the human body to infection requires more energy, mainly directed toward the activation and regeneration of the immune system. This raises the total energy expenditure, which aggravates PEM in malnourished individuals (Fan et al. 2022). The deficiencies in vitamins and amino acids also affect the body's functioning; however, PEM, more specifically, is associated with poor recovery from diseases and a poorer quality of life, higher morbidity, and mortality (Cederholm et al. 2017). In developing countries, nearly half of the 10.8 million deaths per year among children aged under five are attributed to the co-occurrence of PEM and infections (Echendu et al. 2021), such as pneumonia, diarrhea, malaria, measles, and AIDS (de Vita et al. 2019; UNICEF. 2007). PEM diminishes the chances of survival after exposure to fatal infectious diseases and may lead to stunted growth following nonfatal infections. In malnourished children, the risk of infectious morbidity and mortality can be higher.

As mentioned previously, CAP technologies are a highly effective tool against infections caused by bacteria, fungi, and viruses, with the capacity to replace or enhance the efficacy of traditional decontamination agents. The mechanisms behind CAP

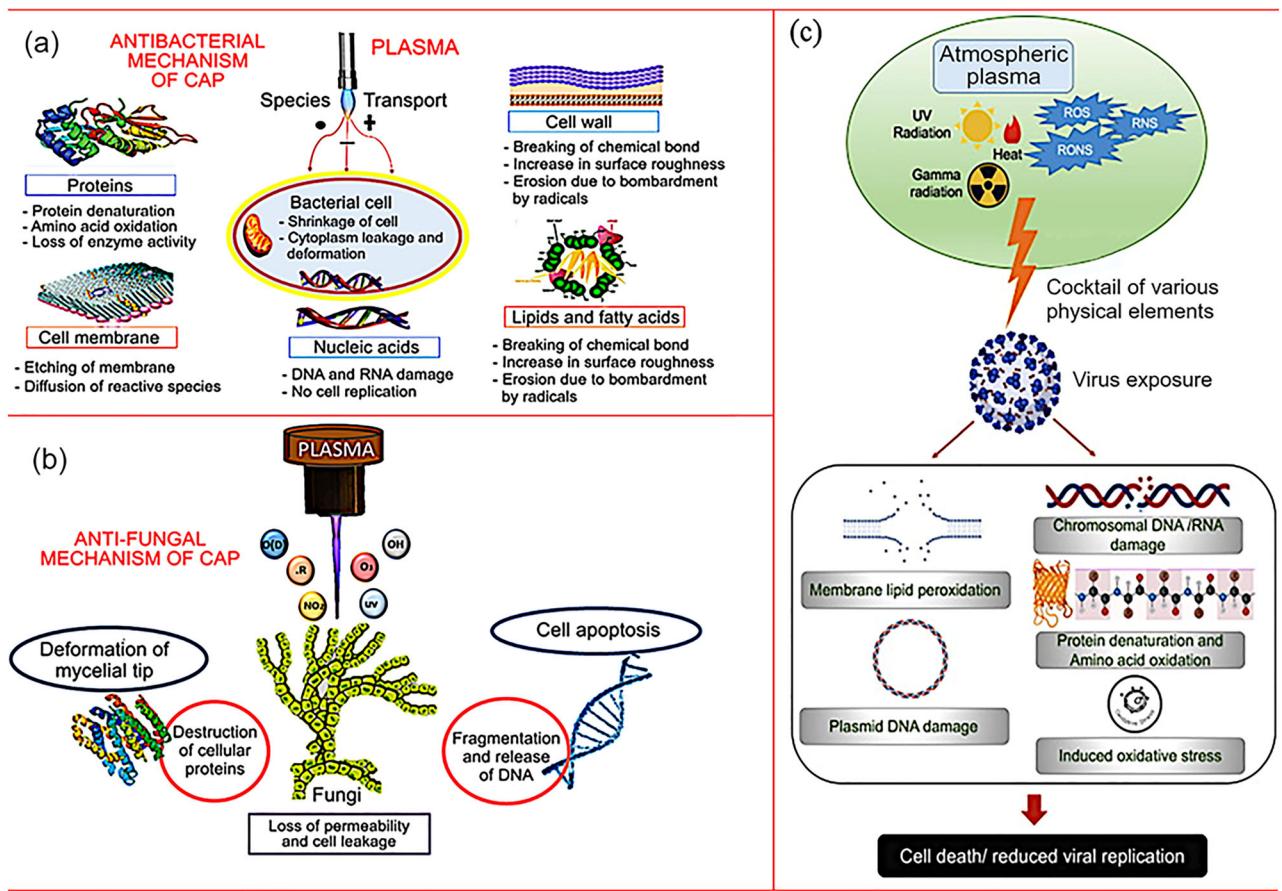


FIGURE 9 | Antimicrobial effects of CAP. (a) Mechanisms by which plasma kills bacteria, (b) fungi, and (c) viruses. (a) is reproduced with permission from reference (Sasi et al. 2023). Copyright (2022) Elsevier. (b) is reproduced with permission from reference (Kaushik et al. 2023) under the terms and conditions of the CC BY license. Copyright (2022) the Authors.

antibacterial activity are diverse. Their relative contribution is highly dependent on the CAP system and operating parameters, for example, gas chemistry and plasma intensity, the nature of the treatment protocol, and the properties of both the surface undergoing the treatment and the infectious agent. The primary agents of this antibacterial action are the reactive oxygen species (ROS) and reactive nitrogen species (RNS) generated during the plasma discharge process, sometimes referred to as RONS. Among the most biochemically active and best-studied reactive species are hydroxyl radicals ($\cdot\text{OH}$), superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), nitric oxide (NO), and peroxynitrite (ONOO^-) (Jiang et al. 2024; Recek et al. 2018; Zhou et al. 2020). These highly reactive molecules can cause extensive damage to bacterial cells through oxidative stress.

The generated ROS and RNS can attack and disrupt the lipids and proteins in bacterial cell walls and membranes. Such a disruption compromises the structural integrity of the bacterial cells, increasing their permeability and finally bringing about lysis. Gram-positive bacteria, with their thick peptidoglycan layers, and Gram-negative bacteria, with their outer membrane and thinner peptidoglycan layer, both succumb to the oxidative damage inflicted by CAP (Figure 9a) (Isbary et al. 2013; Prasad et al. 2023; Zhang et al. 2023). Subsequent to cell membrane disruption, CAP releases reactive species that can penetrate and cause intracellular damage to nucleic acids, proteins, and enzymes involved in

metabolism and replication. Oxidative damage in DNA impairs bacterial replication, while oxidation of proteins impairs vital processes, leading to cell death (Chen and Wirz 2021).

Fungal infections, specifically in immunocompromised patients, are a serious health issue. CAP's antifungal activity, in this aspect, could be explained by the generation of RONS that attack cell walls and components of the fungal cells (Sasi et al. 2023; Sun et al. 2011). Similar to bacterial disinfection, the RONS in CAP disrupt the cell wall of fungi, which is composed of polysaccharides like chitin and glucans, leading to its structural damage and increased permeability (Figure 9b). This increased permeability allows more reactive species to penetrate the cell, causing oxidative damage to nucleic acids, proteins, and lipids. This would inhibit growth and proliferation even in opportunistic pathogens like *Candida* and *Aspergillus* spp. (Leite et al. 2021; Nikmaram et al. 2018).

Viruses pose a unique challenge due to their ability to hijack host cellular machinery for replication. CAP offers a novel approach to inactivating viruses by damaging their protein coats and nucleic acids (Figure 9c), rendering them non-infectious (Sasi et al. 2023). Research has shown that CAP is able to significantly reduce viral loads on living and artificial surfaces and in liquids and aerosols, hence offering a promising means for controlling the spread of viral infections such as influenza, hepatitis, and other emerging

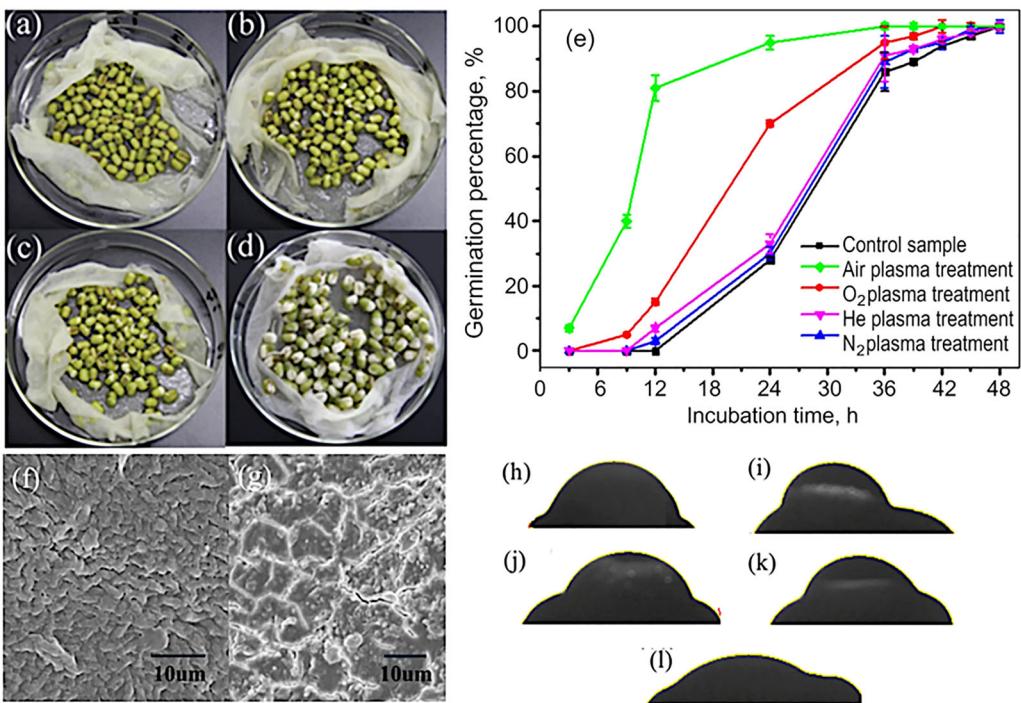


FIGURE 10 | Mung beans treated with air plasma. (a-d) Representative images of mung beans treated with air plasma are shown at different points during the incubation time. (a) 0 h, (b) 9 h, (c) 12 h, (d) 24 h. (e) Germination of seeds treated with He, N₂, air, or O₂ plasma as a function of incubation time. (f, g) SEM images of the surfaces of mung beans (f) before and (g) after air plasma treatment. (h-l) Images of water droplets deposited on the control (h), He plasma-treated (i), O₂ plasma-treated (j), N₂ plasma-treated (k), and air plasma-treated (l) mung bean seeds. Reproduced from Zhou et al. (Zhou et al. 2016) under the terms and conditions of the CC BY license. Copyright the Authors, 2024.

viral threats like COVID-19 (Kaushik et al. 2023). Infection control in healthcare facilities, public places, and transportation may be more effective with disinfection protocols that integrate CAP. This could potentially help to reduce the transmission of viral diseases (Guo et al. 2018).

Thus, with its multifaceted antimicrobial properties, CAP provides an all-inclusive treatment for controlling infections caused by bacteria, fungi, and viruses. The capability to disrupt the integrity of pathogens, plus the adaptability of application, makes it a very valuable addition to the already existing infection control strategies. By integrating CAP into routine disinfection and sterilization processes, we can enhance the safety and hygiene of medical environments, food systems, and public spaces. This, in turn, will contribute to better health outcomes, especially in populations vulnerable to infections due to malnutrition or compromised immunity, ultimately supporting efforts to reduce the global burden of infectious diseases.

5 | Application of CAP for Enhancing Food Safety

5.1 | Protein-rich Plants and Fertilizers

CAP can greatly enhance the growth of protein-rich plants by promoting seed germination and early plant growth (Sivachandiran and Khacef 2017) (Figure 10). Improving the production of secondary metabolites that support plant growth can potentially boost crop resilience to environmental stress, leading to higher protein yield of protein-rich crops (Zhang et al. 2024). CAP can

also improve the amino acid profile of plant-based proteins by enhancing the production of essential amino acids in crops like legumes and cereals. These food sources rich in proteins can address the common challenge of incomplete amino acid profiles in plant-based diets (Langyan et al. 2022; Quintieri et al. 2023). Additionally, by preventing microbial spoilage, the extended shelf life of protein-rich foods, like beans, grains, and dairy products, is reported. This could help in maintaining a stable supply of high-quality protein foods and in mitigation of malnutrition risks (Pan et al. 2019; Pankaj et al. 2018; Yawut et al. 2024) disturb the redox equilibrium in plants, which in turn alters physiological and biochemical processes and activates the chain of signaling pathways and enzymes, ultimately affecting plant growth and development.

CAP finds application in agricultural fertilizers where it is used to enhance the characteristic properties of organic fertilizers through acidification and the addition of reactive nitrogen species (Graves et al. 2019). The introduction of acidic compounds reduces the pH level in the fertilizer, which then promotes the reactive oxygen species to form peroxy nitrous acid (ONOOH). Thus-formed ONOOH decomposes into antimicrobial and oxidizing agents, similar to hydroxyl radicals, leading to the control of bacterial populations and reducing odors. Lower pH conditions reduce ammonia volatilization, increasing nitrogen availability for better retention, and this benefits plant growth by increasing crop protein content (Graves et al. 2019). Nitrogen-enriched organic fertilizer (NEO) is produced by plasma to increase the nitrogen content of the fertilizer and make nitrogen more bioavailable to plants. The effect of NEO on barley and wheat

yield was investigated and compared to mineral fertilizer and plasma untreated slurry (Cottis et al. 2023). The study has shown that mineral fertilizers have about 20% higher nitrogen efficiency compared to NEO, as they require less nitrogen to produce the same yield. However, NEO still represents a significant yield improvement compared to untreated slurry and is a potentially sustainable alternative to conventional fertilizers with lower environmental impacts. In plasma-activated organic fertilizer (PAOF), higher nitrogen content in the form of nitrate (NO_3^-) and nitrite (NO_2^-) is present, which is readily absorbed by plants. Plasma treatment of fertilizer also reduces the emission of greenhouse gases such as methane (CH_4) and nitrous oxide (N_2O), reduces odor and microbial load (Graves et al. 2019). Treatment of bio-contaminated wastewater by bacteria such as *Staphylococcus epidermidis* and *Escherichia coli* with fountain dielectric barrier discharge (FDBD) reactor is focused on producing plasma-activated water (PAW), which can be reused in sustainable agriculture as a fertilizer and to enhance seed germination.

5.2 | Symbiotic Farming Techniques

FDBD plasma treatment reduced bacterial populations up to 7-log in wastewater, which is attributed to the reactive oxygen and nitrogen species (RONS), hydrogen peroxide (H_2O_2), nitrites (NO_2^-), and nitrates (NO_3^-) created by plasma. Nitrates and nitrites enhance germination and plant growth when used as fertilizers (Kooshki et al. 2023). Plasma-generated dinitrogen pentoxide (N_2O_5) gas is produced from atmospheric nitrogen and oxygen via a portable plasma device that utilizes only air as a raw material. N_2O_5 gas served as a nitrogen fertilizer for plant growth. In the study, the effects of N_2O_5 on *Arabidopsis thaliana* were compared with conventional nitrogen sources. Plasma-generated N_2O_5 , when dissolved in a plant growth medium, successfully promoted the growth of nitrogen-deficient plants like *Arabidopsis thaliana*. N_2O_5 was able to replace traditional nitrogen sources and could be used as a nitrogen fertilizer in areas where conventional nitrogen fertilizers are costly or unavailable. This approach could help address global agricultural challenges by providing a sustainable nitrogen source with minimal environmental impact.

CAP integrated into symbiotic systems, like aquaponics (Figure 11), offers a promising strategy to address PEM in regions with limited food availability (Sasi et al. 2023). The complex mixture of reactive species, including ions, electrons, and free radicals produced by CAP, holds strong oxidizing and reducing properties, capable of interacting with biological systems in ways that can significantly benefit both aquatic and plant life within aquaponic ecosystems (Sasi et al. 2023).

The impacts of the CAP on aquatic species are numerous. The generated ROS will efficiently inactivate pathogens that can lead to disease outbreaks and cause high mortality in aquaculture. Improved water quality will lead to improved fish health, resulting in better stock growth and survival (Sangwang and Matra, 2022; Zhou et al. 2019). Furthermore, treatment by CAP does not have an adverse effect on the immune response of fish but makes them more resistant to infections. Apart from controlling the disease, there is a possibility that CAP partially promotes wound healing and fast tissue regeneration, especially for wounded fish

(Bekeschus et al. 2021; Nam et al. 2017). However, further research is needed to clearly explain the mechanisms involved.

CAP has also shown potential in increasing the growth and development of plants. One of the main modes of action includes the creation of reactive nitrogen species, which act as signaling molecules for several physiological responses in plants grown in liquids, including stimulation of photosynthesis, improved nutrient uptake, and stress tolerance (Bozhanova et al. 2024). In this way, through such stimulation of plant growth and development, CAP can increase yields and improve crop quality in an aquaponics system. CAP-generated reactive species have been shown to interact with root cells, stimulating growth and development and promoting root elongation and branching, leading to a more extensive root system (Abeysingha et al. 2024; Sultan et al. 2024). The formed RONS could easily degrade complex organic matter in the hydroponic solution, making essential nutrients available in forms ready for uptake by plants (Adhikari et al. 2019; Adhikari et al. 2020). This can benefit plant growth and water quality since more efficient usage of nutrients reduces nutrient leaching.

Moreover, in the aquaponics system, CAP can efficiently decompose organic waste in the contaminated water, including recalcitrant matter. The major waste present within an aquaponics system is excess fish feed, excreta from aquatic organisms, and breakdown products from dead organisms (Cygowski et al. 2024; Sasi et al. 2023; Wang et al. 2024). These pollutants further deteriorate water quality and fish health, reduce the growth rate of plants and fish, and lower the quality of produce with respect to their color, texture, taste, and safety. In addition, such pollutants increase the adsorption of organic material and complex heavy metals (Cygowski et al. 2024). CAP treatment can also initiate the degradation of pharmaceutical drugs, such as antibiotics, whose persistence is quite harmful to fish stocks and, thus, to the consumer (Rathore et al. 2024). Their presence can lead to the development of antibiotic-resistant bacteria, which can become a serious health risk. Good water quality, healthy fish and plants, and safe and quality produce can be assured with the application of CAP in aquaponics.

By significantly enhancing both fish and plant growth, CAP-treated aquaponic systems generate a more nutritious food source. Fish, a primary protein source, can thus exhibit accelerated growth rates, resulting in increased biomass production. Simultaneously, plants, rich in essential vitamins, minerals, and carbohydrates, can also contribute to a balanced diet. This combined output addresses a critical aspect of PEM by providing a readily accessible and sustainable source of protein and essential nutrients.

5.3 | Efficient Animal Source of Protein Based on Feed Conversion Ratio

Improving livestock feed: CAP could be applied to animal feed, enhancing amino acid content and bioactivity in fodder. By improving the nutritional quality of livestock feed, the quality of animal-derived protein (meat, milk, eggs) could be improved, indirectly helping to address protein malnutrition in human populations dependent on these food sources.

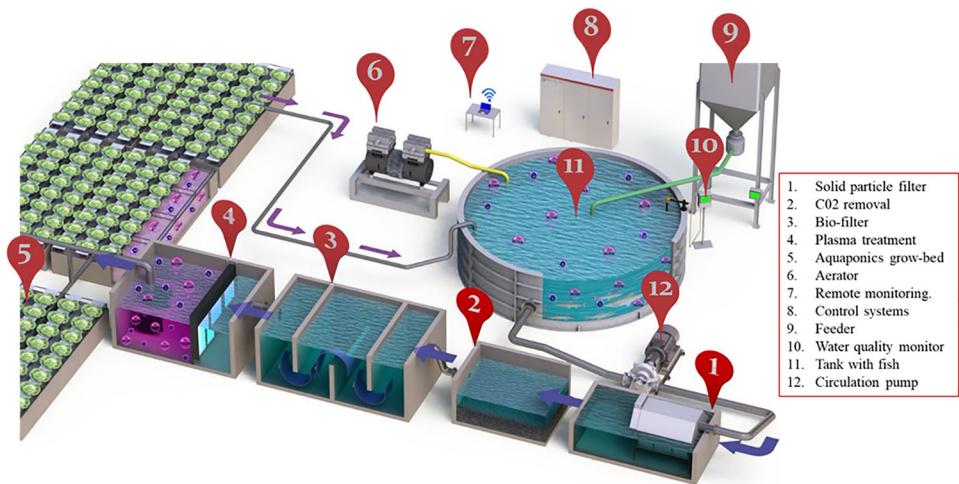


FIGURE 11 | Schematic representation of a fully automated aquaponics system with an integrated plasma treatment chamber. The system includes various components such as fish tanks, grow beds, water pumps, biofilters, and a plasma treatment chamber. The integrated plasma treatment chamber is designed to enhance water quality and nutrient availability, ensuring optimal growth conditions for both fish and plants. Automation includes sensors and control systems for monitoring and adjusting parameters like pH, temperature, and nutrient levels, ensuring the system operates efficiently and sustainably.

While protein is sourced from both animal and plant-based foods, the higher bioavailability of animal protein often necessitates its inclusion in the fight against PEM (Sheffield et al. 2024). Considering the feed conversion ratio (FCR) and protein retention ratio, fish and poultry become highly efficient protein sources. The species grows relatively fast, and their production cycles are short with a low carbon footprint compared to other protein sources (Nijdam et al. 2012). Farmed fish and chicken typically have an FCR ranging from 1.0 to 2.4 and 1.7–2.0, which is notably lower than that of beef cattle (6.0–10.0) and pigs (2.7–5.0) (Fry et al. 2018). With better FCR and protein retention efficiency, more of the ingested feed is converted into consumable protein (Fry et al. 2018). Moreover, chickens exhibit extremely high protein retention rates, with most of the protein ingested by these birds then converted into consumable meat. Thus, both fish and poultry are considerable sources of preventing PEM globally, particularly in resource-poor environments. CAP offers an opportunity to further enhance the efficiency and sustainability of production in both cases.

Studies on the caudal fin and embryo of the zebrafish demonstrated that argon plasma jet (Ar-PJ) has no adverse effects on fin regeneration and embryogenesis in zebrafish; moreover, marginal growth increase has been seen in the fish treated with argon plasma (Nam et al. 2017). This indicates that Ar-PJ does not interrupt but promotes the multiple physiological and molecular pathways governing living organisms (Figures 12 and 13). The biosafety of Ar-PJ was also addressed by studying the embryogenic developmental system of zebrafish (Nam et al. 2017).

A study on poultry demonstrates the potential of CAP to enhance production yield in chicken farms, including vaccine production, growth, and reproduction enhancement. It is a promising tool for enhancing the food safety, shelf-life, and microbiological quality of poultry products, including chicken meat and eggs. The study

shows the effective inactivation of various pathogens, including *Salmonella*, *Listeria monocytogenes*, *Campylobacter jejuni*, and *Escherichia coli*, commonly associated with poultry products. (Gavahian et al. 2019). Additionally, it is observed that a lower voltage and duration of plasma exposure improved embryonic development in chicken, while higher doses were lethal. Low plasma dosages increase cell proliferation and limb growth, while higher doses have anti-proliferative effects and decrease the number of viable cells with induced toxicity, resulting in an increase in apoptosis (Figure 14a) (Zhang et al. 2017). The plasma-generated ROS diffuses through the pores in the eggshell and affects cellular processes. At high doses, the plasma treatment will enhance ROS accumulation, break antioxidant signal pathways, reduce ATP generation, and lower growth factors, thus resulting in embryonic death (Zhang et al. 2017). Furthermore, it is also observed that appropriate plasma treatment before hatching can improve the postnatal growth rates in chickens. For instance, 11.7 kV treatment with non-thermal dielectric barrier discharge plasma for 2 min of the embryos at the Hamburger Hamilton stage 20 can enhance growth rate, tibia length, and metabolic improvements, mainly in males (Figure 14b). Plasma-treated chickens showed enhanced levels of serum growth hormone, insulin-like growth factor 1, thyroid hormones, testosterone, and ATP (Zhang et al. 2018, Zhang et al. 2018). CAP treatment ensures that more poultry protein sources are available and safe for consumption, thus contributing to better overall nutrition and the mitigation of PEM.

6 | Challenges and Future Directions

This review has demonstrated that CAP and PAW represent a family of promising non-thermal technologies that are relatively simple and energy efficient in their design, can be integrated into the existing food production and processing technologies, and as such have a strong potential for enhancing food safety and nutritional quality. While current literature establishes the

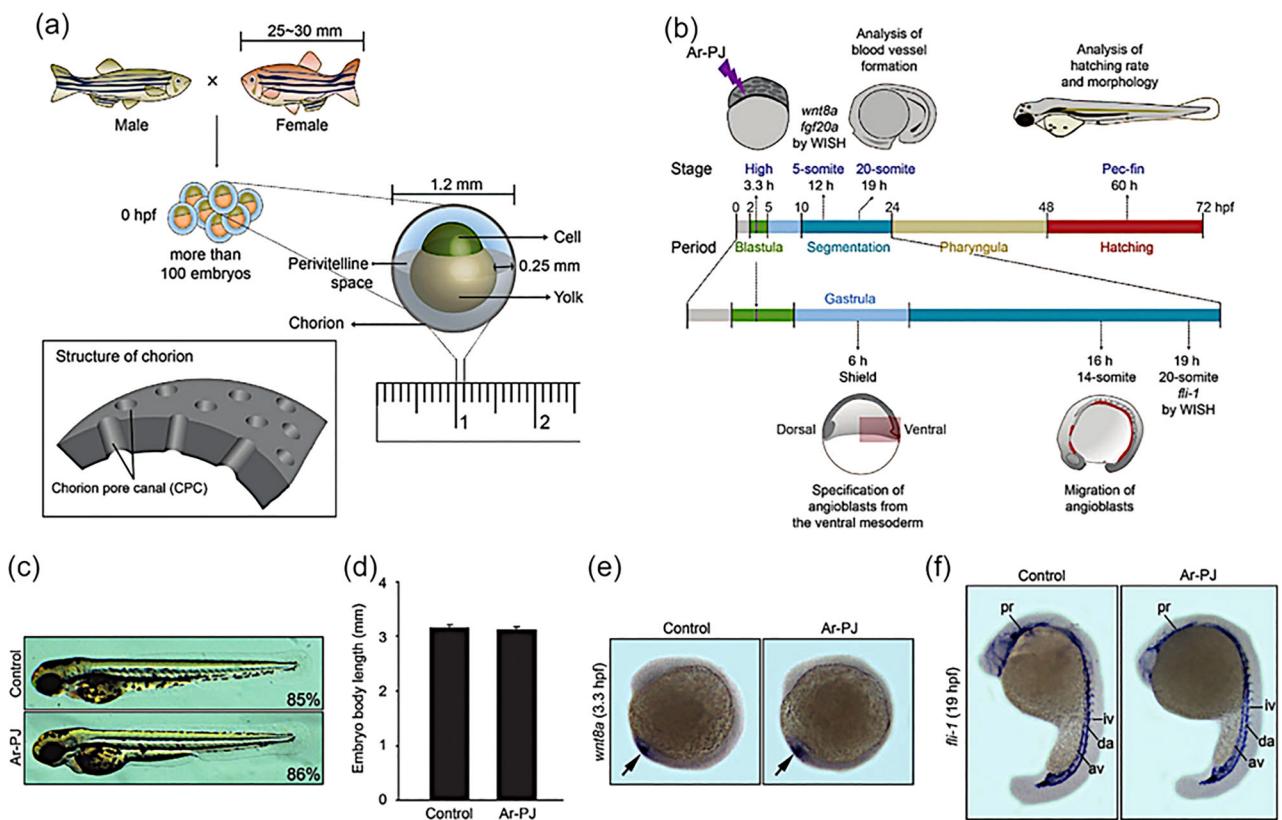


FIGURE 12 | Evaluation of biosafety of argon plasma jet using zebrafish embryogenesis as a novel evaluation system. (a) Schematic diagrams: Zebrafish fertilization and embryo structure at 0 h post-fertilization (hpf). (b) Schematics showing the methods used to examine zebrafish embryogenesis in response to treatment with argon plasma. (c) Embryogenesis completion: Larval hatchability at 60 hpf as an indication of argon plasma biosafety was measured as the percentage of hatched embryos. (d) Body length measurement: Lateral length of the embryo at 60 hpf used as an indicator of biosafety. (e) Cellular level evaluation: Zebrafish embryos which are treated with argon plasma at the blastula stage (3.3 hpf) have undergone whole-mount in situ hybridization. (f) Blood vessel morphogenesis: Vasculogenesis was checked. Vasculogenic sites are indicated: pharyngeal (pr), dorsal aorta (da), axial vein (av), intersegmental vessels (iv), and intermediate cell mass (icm). Reproduced with permission from (Nam et al. 2017) under the terms and conditions of CC BY license. Copyright The Authors, 2017.

capacity of CAP to effectively inactivate microbes, detoxify anti-nutrients, and beneficially modify protein structure, often at competitive energy costs, significant technical, regulatory, and validation hurdles remain. Future progress is critically dependent on addressing the fundamental limitations of low throughput and limited penetration depth of many of the currently developed experimental set-ups through careful engineering of optimized flow-through systems, establishing standardized operating protocols for reproducibility, and generating *in vivo* and clinical data to move beyond lab-scale *in vitro* results and secure widespread regulatory approval. It is worth noting here that the scale-up of CAP systems has been a subject of intense efforts both in academia and in industry, in part because of the wide range of potential applications, particularly in agriculture and water remediation, and in part because it is a considerable engineering challenge due to inherent plasma non-uniformity and instabilities, significant spatial and temporal gradients in, for example, plasma-generated chemical species and heat, limited penetration of species into the food matrices, sensitivity to inherent environmental (e.g., ambient humidity and temperature, air composition, etc.) and food (e.g., moisture content) variables, and importantly, energy efficiency.

Furthermore, establishing model foods and standardized CAP treatment protocols would be a major step toward harmonizing research outputs and enabling cross-study comparisons. Examples of foods that represent important sources of nutrition for large segments of population, and therefore could be used as benchmark “model” foods for the study of the effects of different CAP system configurations and treatment protocols are shown in Table 5. A similar approach can be used to agree on a set of reference protocols that could be used to study the biochemical changes that exposure to a pre-set cocktail of CAP-generated effects induces to better understand the impact of different food sources, or foods at different stages of their processing, on the treatment outcomes. These protocols can also be used as a starting point for process and treatment system optimization, enabling a direct comparison of, for example, treatment efficiency, for a specific family of systems. For *in vitro*, *in vivo*, pre-clinical and clinical studies, it would be important to identify a select number of pairings between “model” processed foods the properties of which are less variable when compared to raw produce, and standardized treatment protocols that have been shown to deliver desirable nutritionally-relevant changes, such as those outlined in Table 6.

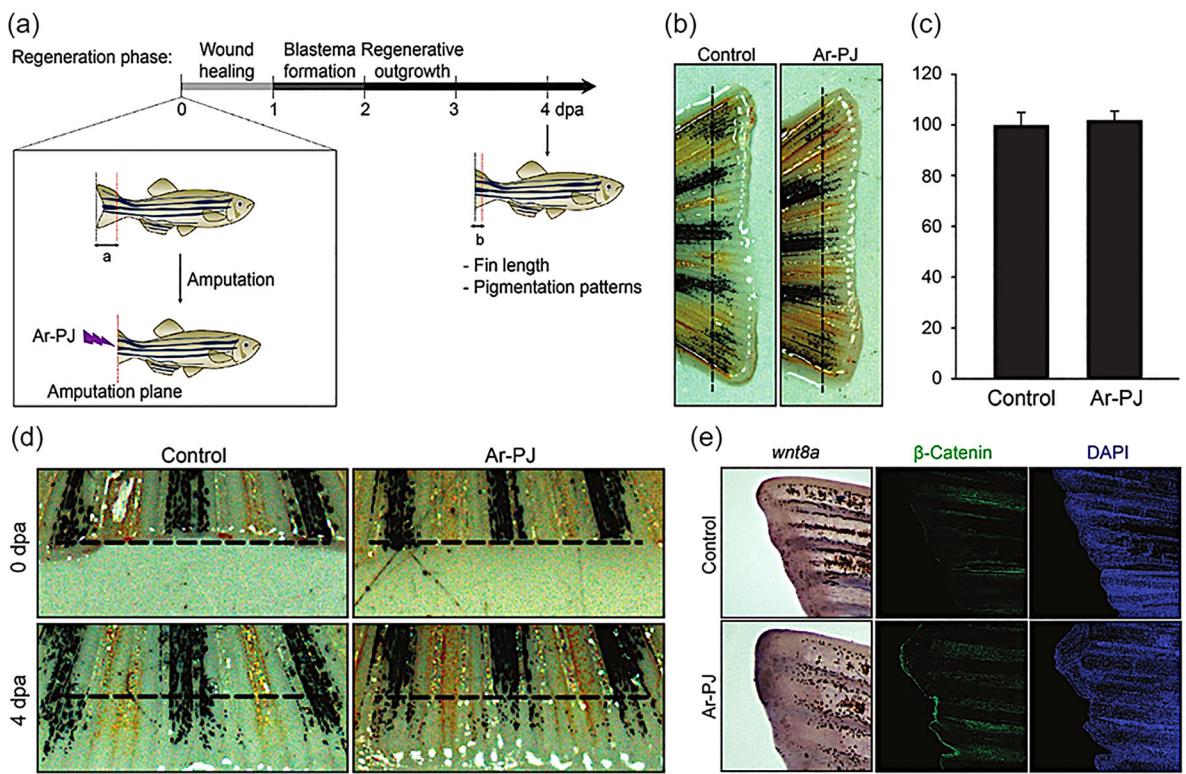


FIGURE 13 | Experimental demonstration of biosafety of the argon plasma jet in living tissues by using the regenerative potential of the zebrafish caudal fin as a new evaluation system. The core elements of this work area. (a) Experimental design: Caudal fin amputation was performed in zebrafish, followed by 30 30-s treatment with argon plasma, followed by incubation at 33°C. Measurements from the amputation plane to the distal tip of the original and newly forming fins are shown. (b) Regrowth rate: The regrowth of amputated fins was photographed and measured at 4 dpa. Such rate features are an indicator of Ar-PJ biosafety in tissue networks. (c) Quantification of regrowth: The regrowth rate was quantified by the ratio of the new fin length to the original fin length in percentage terms related to the untreated control. Data are mean values \pm s.e.m. ($n = 6$). (d) Pigment Cell Patterns: How melanocytes and xanthophore cells were situated within regenerating fins was observed as a measure of cellular network biosafety. (e) Gene detection: The expression of regeneration-associated genes, *wnt8* and β -catenin, in the regenerating fins was examined. Reproduced from (Nam et al. 2017) under the terms and conditions of the CC BY license. Copyright the Authors, 2017.

While the listed examples are predominantly powdered matrices selected for their nutritional relevance and experimental reproducibility, future benchmarking should incorporate more diverse food matrices (liquid, moist, and solid forms such as milk, meat, shrimp, and legumes) to capture the full range of CAP-food interactions.)

Protein-energy malnutrition remains a pervasive global health burden, disproportionately impacting children, pregnant and lactating women, and other at-risk groups. Effective intervention requires not only greater caloric supply but, most importantly, access to high-quality proteins delivering all nine indispensable amino acids that the human body cannot synthesize. Enhancing protein bioavailability and digestibility is therefore central to any PEM-reduction strategy. Cold atmospheric plasma offers a multifaceted approach by modifying protein structures, degrading antinutritional factors, inactivating pathogens, and potentially stimulating nutrient uptake; yet its translation to practical PEM therapies depends on resolving key challenges in quantitative dosimetry, reaction-mechanism elucidation, reactor scalability and safety validation.

6.1 | Quantitative Dosimetry and Standardization

A key impediment to the maturation of CAP technologies is the lack of quantitative standardization. Across the literature, fundamental plasma parameters such as electron temperature, gas temperature, power density, gas composition, and reactive-species fluxes are reported inconsistently or not at all. As a result, reproducing microbial-kill rates or protein-modification outcomes in a different laboratory becomes guesswork. Moving forward, CAP research must adopt SI-traceable “plasma-dose” metrics such as, for example, $\mu\text{mol}\cdot\text{cm}^{-2}\cdot\text{s}^{-1}$ of hydrogen-peroxide-equivalent flux, directly correlated with benchmark bio-effects (e.g., 6-log bacterial inactivation, specific shifts in protein solubility or allergenicity indices). Achieving this will require standard probes for short-lived radicals ($\cdot\text{OH}$, O_2^- , NO) via spin-trap EPR or molecular-reporter assays, alongside agreed electrical diagnostics (voltage-current phase measurements, impedance spectra) to characterize discharge regimes unambiguously. To enable SI-traceable, comparable dose response science, we therefore recommend that CAP studies report a concrete numeric dosimetry set for every experiment. At minimum include elec-

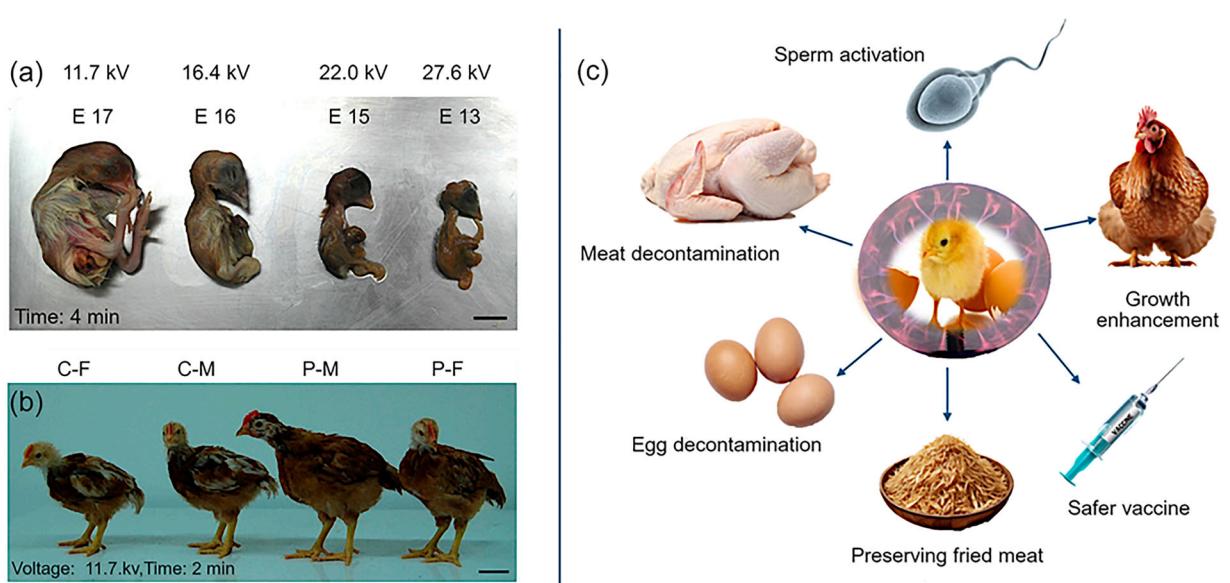


FIGURE 14 | Effects of non-thermal dielectric barrier discharge (DBD) plasma treatment on chicken development. (a) Chicken embryos at a specific developmental stage (HH20) were exposed to different levels of cold plasma for a fixed duration (4 min). The impact of plasma exposure on embryonic development was assessed by monitoring the stage at which embryos died (E is the embryonic day). (b) Chickens hatched from plasma-treated eggs were compared to a control group to evaluate the long-term effects of plasma treatment on growth and development. Physical measurements and hormone levels were assessed at 30 days of age. C-F represents the female chicken in the control group; C-M represents the male chicken in the control group; P-M represents the male chicken in the plasma treatment group. P-F represents female chickens in the plasma treatment group. Reproduced from (Zhang et al. 2018) - under the terms and conditions of the CC BY license. Copyright (2018) the Authors. (c) Different uses of CAP technologies in poultry.

TABLE 5 | Examples of food sources that can be used as “model” foods to benchmark CAP research. These foods are widely consumed, nutritionally relevant, and represent diverse food matrices.

Benchmark food	Rationale	Matrix type
Soy protein isolate drink	High-protein, plant-based beverage; common allergen; low solubility baseline	Reconstituted liquid
Chickpea flour	Rich in protein and fiber; used in gluten-free and traditional diets	Powder
Milk powder	Nutritionally dense; contains allergenic proteins (e.g., β -lactoglobulin)	Powder
Egg white protein	High bioavailability; foaming and gelation properties	Powder
Whey protein concentrate	Popular supplement; sensitive to aggregation and has allergenicity potential	Powder
Spirulina powder	Functional food with prebiotic potential; cell wall disruption improves bioaccessibility	Powder

trical and energy metrics (power-supply type/model; applied voltage peak, for example, 7 kV peak/3.5 kV; current 25 mA; frequency 20 kHz; duty cycle/pulse width - 10%/5 μ s; delivered power - 40 W; power density - 0.40 W·cm⁻²; integrated energy dose per area and volume, e.g., 5 J·cm⁻² or 0.05 kWh·L⁻¹), gas and flow descriptors (carrier gas—e.g., air, purity; flow 1.5 SLM), geometry/exposure descriptors (nozzle size 2.0 mm; inter-electrode gap 3 mm; jet-to-target distance 10 mm; electrode area 100 cm²), treatment metrics (total exposure 300 s, scan speed 2 cm·s⁻¹, time or duration), and sample presentation (sample area 20 cm², sample volume 50 mL, sample mass 25 g, packing density 0.50 g·cm⁻² for bulk solids). Record thermal history with sensor type and placement (e.g., K-type thermocouple at

surface center; contact probe 2 mm depth; report start/peak/end temperatures. Crucially, pair physical descriptors with chemistry: report long-lived RONS at the target (H₂O₂, NO₂⁻, NO₃⁻ in μ M or mg·L⁻¹ and sampling times—example targets H₂O₂ 50–200 mg·L⁻¹; NO₂⁻/NO₃⁻ 50–500 mg·L⁻¹) and, where possible, short-lived species as flux or proxy (\bullet OH flux 0.5–5 μ mol·cm⁻²·s⁻¹ measured via spin-trap EPR or validated chemical reporters). Include representative diagnostics (voltage-current oscilloscope traces, impedance spectra, calibrated OES), the number of replicates (biological n = 3, technical n = 3) and uncertainty, and at least one benchmark dose-response linking a numeric dose to an outcome (for example: $-3 \log$ CFU at 5 J·cm⁻²; Δ DH +12% at 0.05 kWh·L⁻²). Reporting these numeric, SI-traceable

TABLE 6 | Standardized CAP treatment protocols.

Food	CAP setup	Key parameters	Expected outcomes
Soy isolate drink	DBD, ambient air	20 kV, 10 min, 100 mL volume	↑ Solubility, ↓ allergenicity, ↑ dispersibility
Chickpea flour	Plasma jet, argon gas	250 W, 5 min, 1 g sample	↑ Surface hydrophilicity, ↑ digestibility
Milk powder	DBD, He/O ₂ mixture	80:20 ratio, 120 s, 10 g powder	↓ IgE binding (β -lactoglobulin), ↑ solubility
Egg white protein	Helium plasma, continuous flow	50 mL/min, 8–24 min	↑ Foaming capacity, ↑ gel strength
Whey protein concentrate	Gliding arc discharge, open air	15 min, 20 kV, 5 g sample	↑ Antioxidant capacity, ↓ aggregation
Spirulina powder	DBD, ambient air	60 kV, 420 s, 2 g sample	↑ Nutrient bioaccessibility, ↑ prebiotic effect

To ensure reproducibility, each benchmark food should be paired with a well-defined CAP protocol.

items together in a single device-parameters table will convert qualitative descriptions into reproducible plasma-dose science and enable rigorous cross-laboratory synthesis, safety assessment, and regulatory evaluation.

6.2 | Mapping of RONS/Biomolecule Interactions

The second challenge lies in the elucidation of RONS–biomolecule interactions under cold, atmospheric-pressure conditions. Although hydroxyl radicals, superoxide, nitric oxide, and peroxy nitrite are recognized as the principal bioactive agents, their reaction pathways and kinetics in complex matrices—foods, mucosal layers, or soil slurries—remain incompletely mapped. Critical knowledge gaps include rate constants for individual radicals with amino-acid side-chains (e.g., tryptophan, cysteine oxidation), the diffusion lengths and lifetimes of RONS across plasma–liquid and plasma–solid interfaces, and secondary reaction cascades such as nitration of proteins by ONOO[−]. To resolve these, future studies should combine time-resolved optical emission/absorption spectroscopy with high-resolution mass spectrometry to “fingerprint” oxidized biomolecular species and feed kinetic data into predictive reaction models.

6.3 | Scaling and Reactor Engineering

Translating bench-scale reactor designs (DBD plates, APP jets, pin-to-plate arrays) into deployable systems for community-level food, water, and seed treatment presents formidable engineering hurdles. Most prototypes rely on noble gases (He, Ar) and high-voltage benchtop power supplies, thwarting field use in resource-constrained regions. Practical CAP units must therefore operate on ambient air, draw modest power ($\leq 10 \text{ W} \cdot \text{cm}^{-2}$) from compact, solar-compatible electronics, and employ electrode materials and geometries engineered for long service life under continuous operation. Computational fluid-plasma modeling will be indispensable for eliminating “dead zones” in bulk solids or high-flow liquids and ensuring uniform reactive-species delivery.

6.4 | Integrity and Toxicological Safety

The ability of CAP to induce biochemical changes is closely linked to its ability to generate RONS. However, while highly effective in killing microbes, altering proteins, etc., these RONS may also pose presently unknown and potentially significant risks to the food nutritional integrity. For example, over-exposure of food to RONS can lead to the collateral oxidation (degradation) of essential micronutrients, including Vitamins C and E and polyunsaturated lipids. Furthermore, the plasma’s interaction with the food matrix can produce unintended by-products, such as chloramines or nitrated species. These emergent compounds must be rigorously screened, as they carry the potential for mutagenic or allergenic effects. To manage this risk, a safe operating protocol must be followed whenever CAP is used. In order to develop such protocols, it is essential to conduct further studies including, but not limited to, studies specifically focused on: i) determining nutrient-degradation kinetics under specific plasma doses, ii) targeted and untargeted identification of new compounds using advanced analytical techniques such as LC-MS/MS, iii) conducting chronic-exposure assessments using advanced models, such as organ-on-chip platforms (e.g., gut or skin models, etc.). Table 7 outlines a selection of such studies as a starting point for the discussion on safety. It is also recommended to have a pre-specified safety criterion (e.g., toxicant levels below set limits, no persistent neo-epitopes, and nutrient retention above a defined threshold) in place for progressing to field testing. Furthermore, early engagement with national food-safety authorities is important to ensure all compositional and toxicology data meet regulatory approval requirements.

To navigate the vast parameter space and accelerate optimization, CAP research must embrace computational and data-driven methods. Multi-physics simulations that couple plasma kinetics with fluid dynamics and heat transfer can predict spatial RONS distributions before device fabrication. Machine-learning models trained on high-throughput bioassay datasets (bacterial kill curves, protein digestibility metrics, allergen-binding ELISAs) can then identify optimal treatment “recipes” for specific substrates. Integrating real-time optical feedback—monitoring plasma spectral lines—into closed-loop control systems will permit dynamic adjustment of power or gas composition, main-

TABLE 7 | Suggested safety assessment for CAP treatments.

Focus Area	Suggested assessment	Rationale
Plasma chemistry	Quantification of RONS/PAW metrics (H_2O_2 , $\text{NO}_2^-/\text{NO}_3^-$, O_3 , pH, ORP).	Determines the actual dose of active species delivered to the food.
By-product screening	Targeted and untargeted LC-MS/MS for emergent small molecules and oxidation products.	Identifies and quantifies new, potentially harmful compounds.
Macromolecule damage	Protein oxidation profiling (e.g., carbonyl and nitrotyrosine assays) and lipid oxidation panels (e.g., TBARS/aldehyde assays).	Assesses the structural integrity and potential loss of function for proteins and fats.
Allergenicity	Standardized INFOGEST in-vitro digestion followed by immunological testing (using allergic human sera and basophil activation tests).	Checks if the treatment creates novel epitopes (allergen-like structures) that bind IgE antibodies.
Toxicity	In-vitro/in-vivo toxicology (cell assays, organ-on-chip chronic exposure models, and short/sub-chronic animal studies).	Confirms biological safety over extended exposure periods.

As the toxicology profile of CAP-treated food depends heavily on the specific device, feed gas, exposure dose, and food composition, a standardized, multi-faceted safety assessment is necessary before translation to any food, feed, or water application.

taining target reactive-species doses while minimizing nutrient loss.

6.5 | Targeted Experimental Studies

Finally, targeted experimental studies will validate CAP's utility against protein-energy malnutrition. *Ex vivo* gut simulators (SHIME, ARCOL) can quantify how CAP-treated water or foods reshape microbial communities, short-chain fatty-acid production, and epithelial-barrier function. Systematic epitope mapping of major allergens (peanut Ara h 1, β -lactoglobulin) before and after CAP will quantify loss of IgE/IgG binding sites and detect potential neo-epitopes. Exploring CAP-driven membrane poration or enzyme activation in cell-free bioreactors may unlock on-demand synthesis of essential peptides and amino acids. Field trials employing solar-powered, air-plasma seed-treatment units in staple crops will ultimately determine germination enhancement, yield improvements, and disease suppression under real-world agronomic conditions.

By rigorously quantifying plasma doses, mapping RONS chemistries, engineering scalable reactors, ensuring safety and leveraging computational tools, CAP can mature into a predictive, deployable technology—one capable of bolstering food security, enhancing nutrient bioavailability, and combating protein-energy malnutrition on a global scale.

6.6 | Artificial Intelligence for CAP–protein Research

Integrating artificial intelligence (AI) into CAP protein research can transform empirical experimentation into data-driven precision engineering. Machine learning algorithms can analyze high-throughput datasets on plasma electrical signatures, RONS concentrations, protein oxidation profiles, *in vitro* digestibility metrics and much more to uncover complex, nonlinear relationships between discharge parameters and biomolecular out-

comes. By coupling AI with physics-based plasma simulations, researchers can develop surrogate models that optimize reactor settings in real time to achieve targets such as epitope masking or solubility enhancement while minimizing nutrient degradation. This *in silico* optimization reduces experimental burden and expedites the screening of plasma protocols tailored to specific food matrices and protein sources. In the long term, AI-driven, autonomous plasma platforms will accelerate the deployment of scalable CAP treatments that maximize protein bioavailability, ensure safety, and deliver measurable therapeutic benefits in the fight against protein-energy malnutrition.

CAP technologies hold immense promise for addressing PEM, yet fundamental research and future innovation are needed to overcome current challenges. Technological advancements and interdisciplinary efforts could make CAP an innovative tool to address global food security, healthcare and nutritional approaches, thus significantly contributing to combating PEM.

6.7 | Limitations and Scalability

The evidence for nutritional improvement of foods treated with CAP or PAW is currently confined mostly to the food-matrix level or is derived from *in vitro* assays. Direct human data demonstrating improved absorption, nutrient retention, or positive clinical endpoints (e.g., increased muscle mass or improved PEM scores) are not yet available. Therefore, future research must prioritize *in vivo* studies and human trials to bridge the gap between observed physicochemical changes in the lab and substantiated clinical efficacy. Moreover, current limitations around processing efficiency and throughput presents an opportunity for innovation: the immediate focus must be on engineering next-generation non-thermal CAP systems that can handle the high volume of crops and food needed for large-scale interventions, moving beyond laboratory-scale surface treatment to industrial capacity. Similarly, the currently limited penetration depth needs to be addressed through the development of more advanced treatment protocols and specialized plasma configu-

rations capable of treating the bulk of dense foods, rather than just the surface, which will be essential for deep sterilization and pesticide degradation, and for effective chemical modifications of, for example, nutrients and allergens to make them more accessible or effectively neutralize them, respectively. Finally, the challenge of achieving selectivity of modification, the ability to make precise, targeted changes such as reducing anti-nutrients or enhancing specific compounds without damaging critical vitamins or flavors, is the central focus of ongoing plasma chemistry research, which promises to unlock the full potential of CAP as a highly tunable and specific tool for nutritional upgrading.

6.8 | Regulatory Hurdles

CAP-treated food or processes can be classified as novel foods or foods derived from a novel process. Gaining regulatory approval is a slow, costly, and complex process that requires an extensive, standardized body of toxicology, efficacy, and compositional data to demonstrate that the treatment introduces no harmful by-products and maintains nutritional integrity. The current lack of standardized CAP parameters (e.g., power, gas, dose) across research models further complicates approval, as regulators require clear, reproducible, and validated operating protocols. Furthermore, feasibility, particularly in the context of addressing PEM, faces specific technical and regulatory constraints: the plasma process often generates ozone and nitrogen oxides, requiring engineering controls to ensure worker exposure limits are strictly maintained and the air emissions meet safety standards (e.g., FDA/OSHA limits in the workplace). Consumer acceptance is also tied to clear labeling rules that must be established to differentiate CAP-treated food and address perceptions of chemical processing, which can be critical for widespread adoption in vulnerable populations. These technical and regulatory demands, controlling harmful by-products, ensuring worker safety, and securing consumer trust through clear labeling, directly impact the economic and practical feasibility of deploying CAP technology at the scale needed for PEM interventions.

6.9 | Logistical Challenges

Logistical challenges are concentrated in the areas where PEM is most prevalent. Most lab-based CAP devices demand a stable, reliable power source, which is often unavailable in remote or under-resourced communities. Successfully deploying and maintaining the technology requires steady, low-maintenance systems and the development of local technical expertise for operation and repair, preventing the systems from becoming quickly abandoned due to failure or lack of spare parts. It is worth noting that have been some efforts made to develop small-scale solar- and battery-driven CAP systems.

6.10 | Ethical Challenges

These demand careful consideration to ensure the technology is a genuinely beneficial and sustainable solution, not an imposed external “quick fix.” It is essential to ensure that CAP deployment is cost-effective enough to truly benefit the poorest populations without creating new economic burdens or dependencies.

Furthermore, the technology must be culturally acceptable and transparently communicated to the public to mitigate potential fears and build trust in plasma-treated food. Finally, all impacts of the technology on food quality and human health should be studied.

Author Contributions

Karthika Prasad and Syamlal Sasi: conceptualization, data curation, formal analysis, investigation, writing-original draft, writing-review and editing. **Nina Recek:** data curation, formal analysis, investigation, writing-original draft, writing-review and editing. **Janith Weerasinghe and Elena Ivanova:** supervision, writing-review and editing. **Igor Levchenko:** supervision, data curation, writing-original draft, writing-review and editing. **Katia Alexander:** conceptualization, data curation, investigation, writing-original draft, writing-review and editing supervision and funding acquisition.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

No primary research results, software or code have been included and no new data were generated or analyzed as part of this review.

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