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Review

Recent Developments in the Use of Plasma in Medical Applications

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Abstract: A detailed review of the scientific literature was undertaken to examine the most recent developments in plasma processing in the field of medicine. The first part of the review includes a detailed breakdown of the different types of coatings that can be applied onto medical devices using plasma, with a specific focus on antimicrobial surfaces. The developments in plasma-deposited biocompatibles, drug delivery and adhesive coatings in 2023 are described, and specific applications in additive manufacturing are highlighted. The use of plasma and plasma-activated liquids as standalone therapeutics continues to evolve, and pertinent advances in this field are described. In addition, the combination of plasma medicine with conventional pharmaceutical interventions is reviewed, and key emerging trends are highlighted, including the use of plasma to enhance drug delivery directly into tissue. The potential synergies between plasma medicine and chemotherapeutics for oncology and infection treatment are a growing area, and recent advancements are noted. Finally, the use of plasma to control excess antibiotics and to intentionally degrade such materials in waste streams is described.

Keywords: medicine; cancer; polymerization; coating; 3D printing; surface

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1. Introduction

Plasma processing has a long history in medical applications, and thermal plasma spray has been used for decades to deposit metallic and ceramic coatings onto implant surfaces to enhance functionality and biocompatibility [1]. However, the high temperatures encountered in this process have limited the use of the technique to deposit organic layers or to apply coatings onto thermally sensitive materials. The deposition of functional organic layers has taken longer to develop and is still an emerging science. The earliest deposition of organic layers involved the fragmentation and rearrangement of monomer vapors in a vacuum plasma discharge [2,3]. This produced a deposit with random atomic recombination, which limited deposition to simple layers such as metal oxides or nitrides [4]. Attempts to improve the retention of chemical functionality through downstream plasma deposition [5] or extreme low temperatures [6] proved only mildly effective, and the resultant thin films still contained significant molecular rearrangements, which limited the ability of plasma processing to deposit chemically complex coatings with retention of the original functionality. It was not until the application of pulsed plasma discharges in the 1990s that truly functional polymer films could be deposited in vacuum chambers that retained the functional chemistry of the starting monomers [7–9]. Later attempts to transfer these processes to atmospheric pressure showed that the deposition was highly sensitive to variations in power and flow rate [10], and all of these vapor-based systems required the use of a volatile precursor gas. Despite these limitations, pulsed vacuum plasma processing led to a large number of novel plasma coatings for use in biomedical applications.

The development of aerosol-assisted atmospheric pressure plasma deposition opened the possibility to deposit non-volatile liquids under ambient conditions [11–13]. It was quickly realized that this created the possibility to include dissolved solids and thereby

integrate solid materials into plasma polymer films. Various materials could be incorporated into the growing polymer films if the dissolved material was introduced alongside a monomeric material that was undergoing polymerization. This method was used to deposit antimicrobials [14,15] and also various proteins and enzymes [16–18]. Further advances showed that it was possible to deposit pure coatings without the plasma polymer layer. For example, using a low-temperature plasma, it was possible to directly bond proteins and pharmaceuticals directly onto a range of substrate surfaces [19,20].

It is now possible to deposit coatings onto medical devices using precursors derived from solids, liquids and gases, or even combinations thereof. This reveals wide potential for plasma coatings in temperature-sensitive therapeutic applications, and recent developments in this field are reviewed below.

2. Coating of Medical Devices

Surface modification of medical devices is a market that continues to expand and is presently worth in excess of six billion USD [21]. The market includes a wide variety of applications, but plasma coating is mainly focused on the application of antimicrobial, adhesive, biocompatible and drug delivery applications.

2.1. Deposition of Antimicrobial Films

Antimicrobial coatings are widely applied to medical surfaces to mitigate microbial contamination and thereby minimize infections within the patient. Plasma coatings offer significant advantages here, as the coatings are highly adherent and can be applied as thin films that do not adversely alter the mechanical properties of the medical device. One application of plasma coatings is to deposit adhesive layers, which enhance the attachment of functional coatings. For example, surfaces that are rich in free radicals or other reactive species can be created using plasma treatment to enhance the attachment of antimicrobials [22]. Among the common antimicrobials are silver, natural oils, polydopamine and antibiotics [23–26].

A simple plasma activation is often the first step in depositing a coating. The plasma activation can both clean the surface and produce reactive groups that facilitate the adhesion of functional coatings, as shown in Figure 1. This allows traditional wet chemical techniques to be used to attach coatings to hydrophobic or metallic surfaces that are not easily coated. This method is especially common when attaching polydopamine coatings onto implant surfaces [27–29]. These coatings can then provide biocompatible and antimicrobial properties.

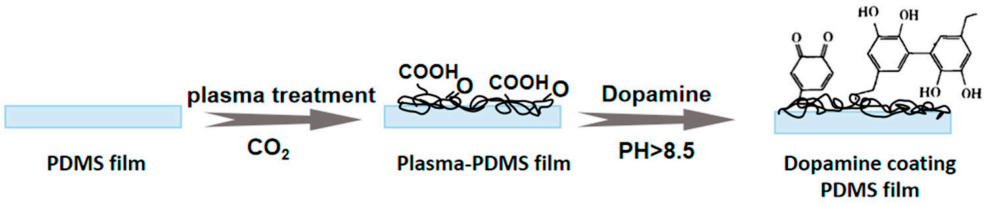

Figure 1. Plasma pre-treatment to prime a surface for subsequent coating. Reprinted from [27].

Plasma can also be used to deposit functional antimicrobial coatings directly in a single-step process. Baculi et al. [24] deposited silver nanoparticles onto fabric samples using an atmospheric pressure plasma jet. The particles retained their antimicrobial properties after deposition and were shown to retain efficacy against a wide variety of bacterial strains [24]. An interesting approach was described by Su et al. [30], who immersed fabrics in silver nitrate solutions and then used an atmospheric pressure plasma jet to induce reactions within the liquid, which caused the silver to be deposited onto the fabric surface. Despite the low doses deposited, the silver proved highly effective against bacterial challenge assays and showed no sign of toxicity, potentially opening up applications in medical fields [30]. Plasma can also be used to form silver nano-particles, and these were co-polymerized

with a siloxane to form a thin film coating and then shown to be effective for microbial control in both in vitro and in vivo assays. Interestingly, the plasma played two roles here: (i) forming the nano-particles and (ii) binding the resultant particles into a growing plasma-polymerized film of siloxane [31].

Various biomolecules have also been deposited as functional coatings using plasma. An antimicrobial peptide was deposited onto a medical-grade titanium alloy by Teixeira, following the plasma polymerization of a primer layer. This allowed the antimicrobial agent to be covalently bonded to the metal surface [32]. Various methods have been attempted to promote the adhesion of chitosan layers to surfaces. These are primarily based on a simple plasma activation of the substrate, followed by the addition of the chitosan layer. This area has been extensively reviewed by Vesel [33]. Chitosan is widely used as a coating due to its inherent antimicrobial and biocompatible properties. A recent study by Ho et al. showed that chitosan and other biomolecules were effectively attached to zirconia using this approach [34]. This could have significance in the area of dental implant integration.

The deposition of natural oils and extracts continues to draw significant interest, and this area was recently reviewed elsewhere [25,26]. The introduction of the oil into the plasma is frequently achieved using a simple bubbler, in which a process gas is fed through the liquid oil and thereby conducts vapors emitted by the oil into the plasma discharge, as shown in Figure 2. Based on this simple concept, the deposition of various Eucalyptus oils [35,36] has proven to be an ongoing area of interest. It is well known that various extracts from the Eucalyptus plant can act as anti-oxidants or antimicrobials [37], and the plasma polymerization of this material has been studied for over 20 years [38]. Bullman et al. [35] applied the material onto medical-grade titanium alloys using a cold plasma process and showed that the surface retained antimicrobial properties while also facilitating the adhesion of mesenchymal stem cells. Kayaian and Hawker used an extract from Eucalyptus oil, termed 1,8-cineole, along with plasma processing to attach this material to wound dressings. They examined how variations in the plasma parameters altered the functionality of the extract. Various duty cycle levels were evaluated in an attempt to retain a higher degree of antimicrobial functional groups when compared to continuous wave deposition [36]. Other natural oils were also deposited using plasma processing, including D-limonene [39] and carvone [40]. Both of these materials were effectively deposited using plasma polymerization at atmospheric pressure and were shown to retain significant antimicrobial activity using in vitro assays. Carvone was also applied onto collagen scaffolds using a plasma process, and this improved the antimicrobial properties of the scaffolds. However, it was observed that careful control of the plasma parameters was required in order to prevent degradation of the collagen scaffolds [41]. Stable carvone films were also achieved by co-polymerizing the material with octadiene, which produced highly stable polymeric films while retaining the antimicrobial and biocompatible features of the natural oil [42]. The combination of plasma with natural chicory extracts has also shown efficacy against multi-drug-resistant bacteria in an in vitro study [43].

Plasma processing also offers a number of applications in the control of drug release. This can vary from simple approaches wherein plasma activates the surface to allow for the elution-controlling layers to be attached [44], to direct plasma deposition of layers that directly control elution. Recent examples include coatings that control the release of antimicrobials from medical devices. Iodine is a widely used and well-understood antimicrobial that can minimize wound infections. Complexing an iodine-containing material with a range of plasma-polymerized materials produced coatings that were biocompatible and could release iodine from a wound dressing over the course of twenty-four hours in a sufficient concentration to kill a number of bacterial pathogens. Altering the plasma polymer produced changes in the iodine loading and release rate [45]. Similarly, it was shown that a plasma-polymerized siloxane layer could improve the performance of silver nano-particles on a medical device. The thin (16 nm) layer maintained the antimicrobial properties of the nano-particles while improving the biocompatibility [46].

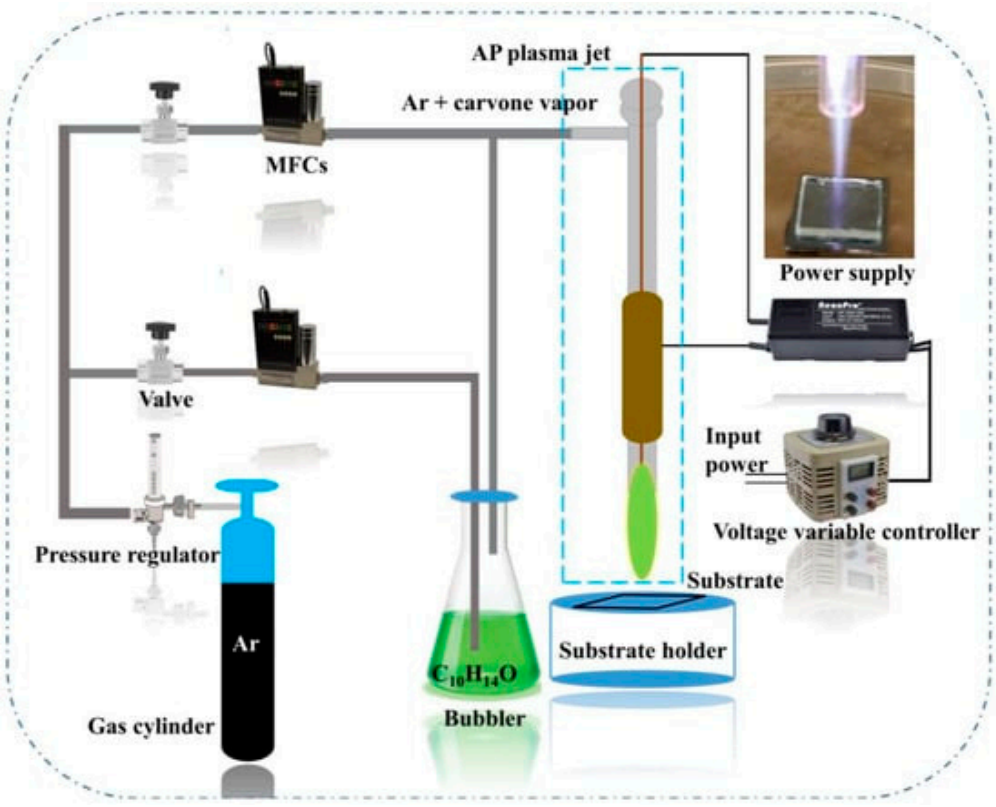

Figure 2. A typical experimental setup for the deposition of essential oils. Reprinted from [40].

2.2. Deposition of Biocompatible and Adhesive Coatings

Plasma-deposited polymer coatings have been widely studied over many years and are now finding widespread use as binding layers that can be used to attach highly functional biologics onto various scaffolds, dressings and medical implants [47–51]. Even simple plasma coatings can have dramatic effects on medical outcomes. Depositing a simple plasma-polymerized allylamine or acrylic acid coating onto a wound dressing significantly impacted wound-healing rates. The impact of the modified dressing was not a simple response, though, and careful consideration should be given as to when modified dressings are used in a healing process [47]. A plasma-polymerized heptylamine coating allowed cells to be attached to silicone dressings, and this allowed the cells to be transferred onto a wound site to accelerate healing [52]. Heptylamine coatings have also been recently shown to enhance the biocompatibility of titanium alloys [51]. A plasma-deposited layer of acrylic acid enhanced the adhesion of platelet-rich plasma onto polycaprolactone fibers. The inclusion of the acid groups enhanced cell adhesion and proliferation [49]. In addition to the materials described above, plasma-deposited allylamine enhanced the adhesion of functional proteins onto ceramic dental implants [50], thereby demonstrating the wide range of materials that can be treated with such an approach. However, it remains necessary to control the pertinent plasma parameters for each system in order to optimize the coating performance [41,53–55].

In addition to acting as a primer layer, the plasma deposit can also be used as the final functional layer, and this continues to attract attention beyond simple antimicrobial coatings. From the earlier coatings of simple antifouling fluorocarbons [56], plasma deposition has now evolved to embrace more complex Zwitterionic antifouling layers [57]. Bio-compatible layers can now be prepared from materials such as organosilicons [55], and plasma processing is a key step in the manufacture of blood-compatible coatings [58]. The development of barrier coatings for a range of medical and non-medical applications is a growing area [59].

Though the application of plasma treatment of medical devices is continuing to grow, there is also widespread use of plasma processing in their additive manufacture. A simple plasma-polymerized allylamine layer was found to improve the cytocompatibility of a three-dimensional (3D)-printed vascular stent [60]. There is an increasing body of emerging work with respect to plasma coatings being used to modify 3D-printed and electrospun devices [61], as shown schematically in Figure 3. Though there are numerous reports of plasma being used to activate or oxidize 3D-printed scaffolds [62], until recently, there have been very few reports of active plasma coatings of such scaffolds [63,64]. The low temperature of the plasma process and ability to penetrate into 3D substrates without risking pores being blocked allows for a positive synergy between the additive manufacturing and plasma processing, and recent research has reported progress in applications as diverse as ion implantation [65], drug monitoring [61], antimicrobial coating [22] and cell growth [66,67]. Asadian et al. [68] reported on the effects of plasma-deposited acrylic acid and allylamine layers to direct cell differentiation on polycaprolactone electrospun meshes. The coatings were uniform and hydrophilic and contained appropriate functional groups to enhance cell growth. The modified surfaces were shown to enhance the cell development and could potentially offer enhanced regeneration of cartilage [68]. Similarly, work by teams led by de Geyter and Morent demonstrated that plasma-functionalized coatings could be deposited onto nanofibers to produce biocompatible surfaces. Their work produced a high density of amine functional groups on a poly(D,L-lactide-co-glycolide)—polycaprolactone fiber mesh and showed that the coatings were uniform, and cell culture studies with Schwann cells demonstrated the enhanced performance of the coated meshes [69]. A separate work showed that the creation of high-density, amine-rich surfaces is key in optimizing cellular responses [70].

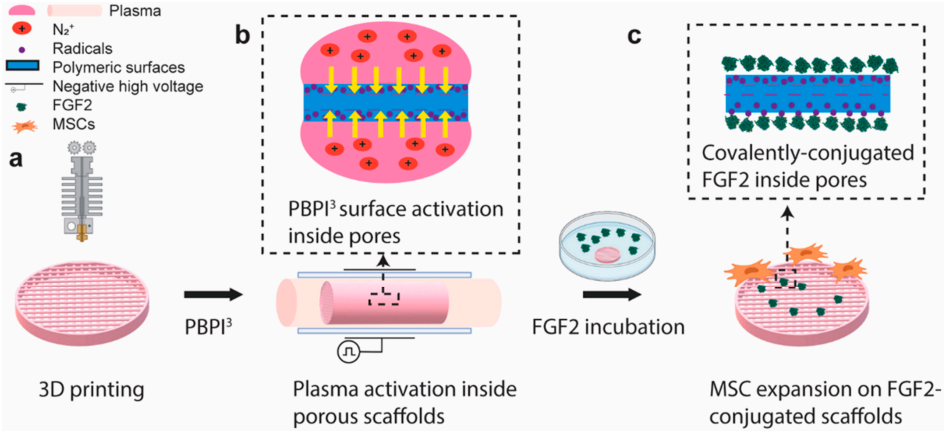

Figure 3. Plasma treatment of 3D-printed surfaces. The steps involve include (**a**) 3D printing of polymer scaffold; (**b**) Plasma activation inside the porous scaffolds and (**c**) Covalent immobilisation of a coating such as FGF2 onto the activated scaffolds. Reprinted from [65] with permission from Elsevier.

One interesting development for implant surface modification is plasma electrochemical oxidation (PEO), which remains an active area of research for biomedical science. PEO offers a facile route to grow a porous ceramic layer on metal surfaces. There remains a wide array of simpler PEO-derived surfaces that can offer antimicrobial properties [71], and PEO layers also offer benefits such as improved biocompatibility and enhanced corrosion and wear resistance [72]. Recent years have seen significant use of multi-layered approaches wherein PEO layers are combined with additional coating layers to produce more advanced functionality. For example, Moreno et al. used PEO to develop a multilayered drug delivery system to deliver a ciprofloxacin antimicrobial. The porous multi-layered coating was capable of eluting drugs for several weeks [73]. Farshid et al. developed a multifunctional coating using a combination of PEO and electrodeposition. Their coating offers a unique combination of corrosion resistance, biocompatibility and self-healing capacity when ap-

plied to magnesium alloys. The electro-deposited top coat of polydopamine was found to protect and enhance the properties of the PEO layer [74]. A related development is the use of plasma-assisted electrochemical synthesis, which has recently allowed the creation of carbon quantum dots with the ability to target cancer cells [75].

3. Plasma as a Therapeutic Intervention

3.1. Direct Application of Plasma to Tissue

Although plasma is used extensively to modify medical device surfaces, it can also be used directly to convey or produce therapeutic effects, and efforts to develop this area have been ongoing for over twenty years. Early work by pioneers such as Eva Stoffels [76,77], Mounir Laroussi [78] and others showed the impact of plasma on bacterial and human cells [79–81]. Non-thermal plasma discharges contain a wide variety of reactive species including ions, free radicals, ultra-violet rays, magnetic fields and various reactive oxygen and nitrogen species. These species can interact with damaged tissue, cancer cells and micro-organisms to produce a wide range of biological responses [82,83]. Though the field of Plasma Medicine is quite new, it continues to grow significantly, and new applications and developments are emerging. It is now an active area of research in dermatology [84], oncology [85,86], surgery [87], wound healing [88,89] and infection control [90]. Though the area is expanding, it must be noted that there remains a paucity of FDA-cleared plasma devices that can be applied in the field of Plasma Medicine. This research field will be restricted until such devices are approved for specific applications based on rigorous clinical trials, proven quality assurance in manufacturing and demonstrated safety, biocompatibility and electrical safety. Despite these challenges, research continues, and the benefits of plasma may yet be employed via indirect approvals. For example, many electrosurgical devices are already cleared for applications that utilize plasma, such as cutting and coagulation, and it is well known that these electrosurgical systems create reactive species [91]. These reactive species are known to be antimicrobial [92]. Yet the antimicrobial benefits of plasma are not claimed in any FDA-approved procedure. Any antimicrobial impacts are often secondary benefits that assist in other applications, such as dermatology or wound healing, without ever being approved by the FDA as an antimicrobial effect. Part of the problem may be in proving that the antimicrobial impact is due to the plasma treatment applied. As the exposure to the plasma discharge is short-lived, the resultant impact may be transitory, and bacterial numbers may recover well following an initial treatment [93].

Though the antimicrobial impacts of plasma discharges are not as long-lasting or as systemic as those that can be achieved using pharmaceutical interventions, plasma discharges do offer a number of benefits, including targeted delivery. In addition, the wide variety of reactive species in the plasma creates an array of diverse antimicrobial mechanisms, and this can reduce the likelihood of bacterial resistance emerging in response to the plasma treatment [92,94,95]. This may be particularly significant as we face growing waves of multi-drug-resistant bacteria [96]. A recent multicenter clinical trial showed that including plasma as a component of wound treatment gave rise to a 210% increase in wound closure. Of particular note was the fact that antibiotic usage in the plasma-treated group was significantly lower (4%) than in the control group (23%), highlighting the potential significance of plasma in combating infection in a clinical setting [97]. This was also supported by various case studies conducted elsewhere in recent publications [98].

3.2. Combinations of Plasma with Traditional Pharmaceuticals

Based on the positive data generated in recent years around the topic of Plasma Medicine, there has been a move towards combining plasma discharges with traditional therapeutic interventions. However, the impact of plasma on pharmaceutical compounds is a highly complex area, and great care must be taken to ensure that the plasma discharge does not either chemically degrade or alter the active pharmaceutical agent. Pharmaceutical compounds contain numerous reactive chemical groups that could be potentially altered by the plasma (Figure 4), thereby altering biological functionality and safety. In addition,

detailed studies are required to ensure that the plasma does not inhibit the uptake or alter the biological pathways that are targeted by the drug. Any such interaction could make the combined treatment less effective. Interestingly, the combination of plasma and traditional pharmaceutical agents can also give rise to additional synergies. For example, it was found that plasma treatment of ethanol solutions produced significant decreases in bacterial numbers, even at ethanol concentrations that were not expected to be effective [99]. Recent studies have suggested that combining antibiotics with plasma can produce dramatic reductions in the minimum inhibitory concentration (MIC) of various antibiotics. Maybin et al. showed that a pre-treatment with sub-lethal doses of plasma produced a 256–512-fold decrease in the MIC of various antibiotics when treating *Pseudomonas aeruginosa* [93]. These effects could be associated with plasma-mediated modifications to the cell envelope [100] or biofilm structures and responses [101] that could facilitate antibiotic effects.

There is a growing interest in the use of cold atmospheric plasma in oncology, and several groups have looked at the combination of plasma and oncology drugs. It was recently shown that specific plasma treatments can be used to convert oncology prodrugs into active pharmaceuticals in vitro [102]. Combinations of either plasma or plasma-activated water with drugs such as Topotecan [103], Tirapazamine [104] or Doxorubicin [105] have been shown to enhance activity in detailed cell culture studies. Dezhpour et al. showed that combinations of plasma and doxorubicin were highly effective in reducing tumors in a rodent model study, and that this combination may decrease the dose of chemotherapeutics needed to produce efficacy in a clinical setting [106]. The combination of plasma and doxorubicin was also studied in a second rodent model, and the plasma process applied enhanced the efficacy of the oncology drug [107]. Similar results were observed in recent preclinical studies on the combination of plasma with cisplatin for the treatment of head and neck tumors [108]. Aside from the direct benefit from the plasma treatment itself, the exposure to the plasma seems to provide various mechanisms to overcome drug resistance [108,109] and to enhance the anti-tumor effects of traditional oncology drugs [106,110], and this can be particularly significant for hard-to-treat cancers. A part of this effect may be caused by the enhanced oxidative stress induced by the plasma species [111].

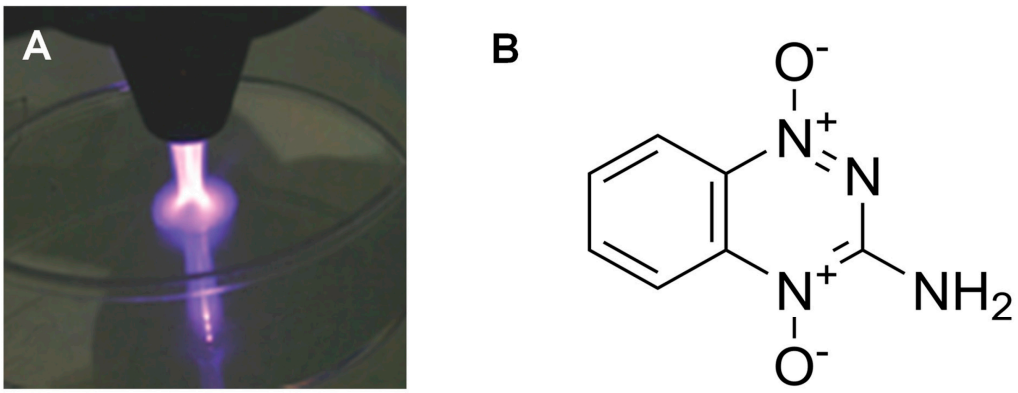

Figure 4. Image of plasma discharge (**A**) and chemical structure of the oncology drug Tirapazamine (**B**). Reprinted from [104].

There is a further emerging interest in the use of plasma discharges to enhance drug delivery via trans-dermal approaches. The plasma discharge can disrupt and possibly even perforate the skin, thereby creating channels that allow for rapid and effective diffusion of therapeutic formulations into the skin. As these perforations are small, they heal and close rapidly, allowing for effective drug delivery [112]. The technique is pain-free, unlike traditional electroporation approaches [113]. A wide range of therapeutics have now been shown to be compatible with this approach [114], and that list continues to grow [115]. Recent studies have focused on the use of plasma-treated hydrogels to deliver prolonged transdermal drug delivery. Early studies indicate that the choice of hydrogel is important

in controlling the drug delivery properties of the treated gel [113]. A related feature was the emergence of drug delivery hydrogels that had been plasma-treated. These can provide an extended release of the therapeutic plasma species [116].

3.3. Interactions of Plasma with Liquids

Plasma can also be used to directly manufacture biologically active solutions, and recent years have seen widespread investigation of plasma-activated water in the treatment of bacterial [117–119], fungal and viral infections [120,121]. Changes in plasma gas composition [117,119], plasma settings [118] or plasma sources [122] can dramatically alter the composition of the treated liquid, and this can give rise to changes in the physical properties of the activated liquid, which may in turn impact performance [123,124]. Other researchers continue to report on the significant impact of PAW and PAS on oncology, with numerous researchers describing the impact of varying the choice of liquid [125], liquid temperature [126] and plasma sources [123,127–130], similar to those noted for antimicrobial applications. Of particular note were the benefits seen from combining plasma-treated solutions with the amino acid tyrosine. This produced greater concentrations of reactive species in solution and a pro-apoptotic effect in multiple cancer cell lines [128].

Most of these approaches are based on the creation of the plasma-treated liquid in a first step and then subsequent deployment after some period of time. Given the potential for degradation and alteration of reactive species profiles in treated liquids over time and in different environmental conditions, this may give rise to variability in functionality. Kutasi et al. reported on potential mechanisms to stabilize the active species in the liquid with varying degrees of success [131]. The development of an in situ system to generate plasma-activated liquids as needed would confer numerous benefits and overcome the need to stabilize the treated liquid. One new technique to achieve this is the creation of plasma-activated nebulized mist (PANM). This technique uses a plasma-activated air source to pneumatically spray a saline mist, and detailed studies have shown that this technique can deliver therapeutically effective doses into the respiratory tract, which could actively reduce bacterial infection [132]. Saadaway et al. described a similar approach to deliver therapeutic doses of PAW mist. They termed their technique as plasma-activated air-driven water mist (PAAWM) and showed that the resultant mist was effective against multiple cancer cell lines in an in vitro study [133].

Of particular interest is the recent development combining PAW with traditional pharmaceutical approaches. It is well established that both bacteria and cancer cells can develop resistance to conventional pharmaceutical treatments. The combination of PAW with such active drugs can produce new pathways to overcome these resistance mechanisms, and this is an area of active research. In oncology, the combination of PAS with traditional drugs could be facilitated due to the increased internal reactive oxygen species within the cell, which renders them more susceptible to the action of the pharmaceutical agents [129]. Pavlik et al. observed this response when combining doxorubicin with PAW [110], and a similar response was observed with Topotecan when used to treat glioblastoma cells [103].

4. Decontamination of Unwanted Pharmaceutical Active Ingredients

One final area of application is the use of non-thermal plasma discharges to actively degrade antibiotics in wastewater. As many antibiotics are not completely broken down enzymatically in human and veterinary applications, this leads to those antibiotics being released into the environment via wastewater. At these low concentrations, they can interact with bacteria at levels below their effective minimum inhibitory concentration. This allows bacteria to develop resistance mechanisms to the antibiotics and can contribute to the overall emergence of additional antibiotic-resistant microbial strains [134]. One possible way to mitigate this is to identify key waste streams and to remove or destroy the antibiotics within such sources before they are discharged into the environment, as shown schematically in Figure 5. Plasma discharges have long been shown to be capable of

eliminating a wide range of antibiotics in wastewater, including tetracycline [135,136], oxytetracycline, doxycycline [137], β-lactams [138], ofloxacin, ampicillin [139,140], amoxicillin, sulfamethoxazole [141,142], sulfadiazine [136,143], levofloxacin [143], norfloxacin [136] and ciprofloxacin [144]. Interestingly, the plasma is also capable of inactivating antibiotic-resistant bacteria and antibiotic-resistant genes in wastewater [145].

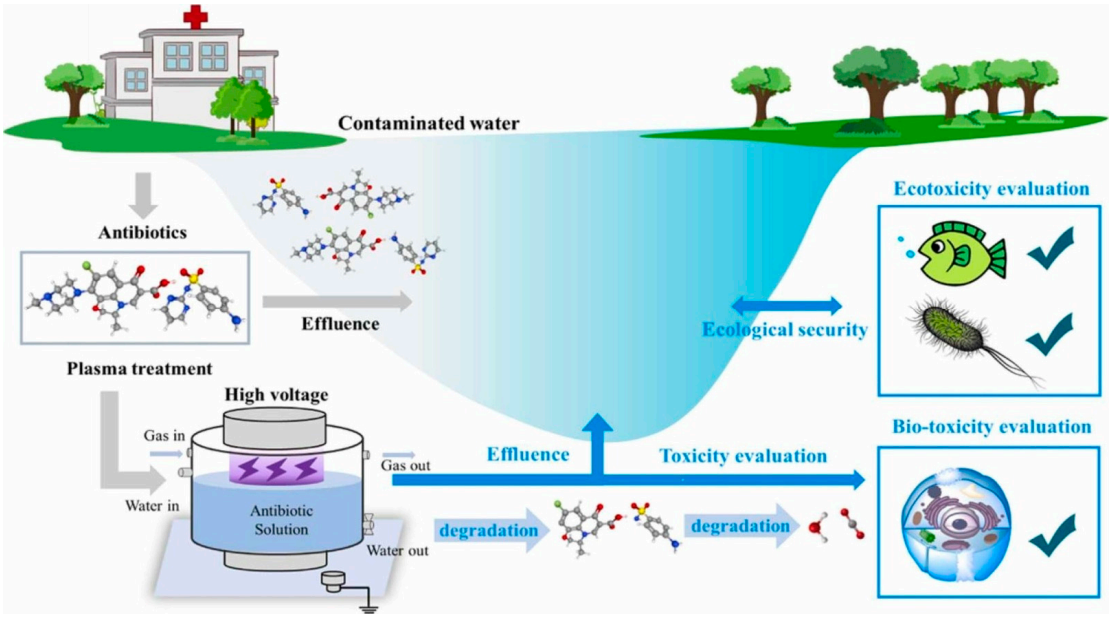

Figure 5. Graphical representation of the use of plasma to remove antibiotics from wastewater. Reprinted from [143] with permission from Elsevier.

Various plasma systems have been proposed for these antibiotic degradation applications. These include various dielectric barrier discharges [141–143], jets or pencils [139] and submerged plasma systems [136,144]. The exact mechanism of degradation will depend upon the choice of plasma system, operating parameters and the chemistry of the antibiotic being treated. However, as a general rule, it can be stated that the plasma produces reactive oxygen and nitrogen species that can react with the antibiotics and produce significant degradation in a matter of minutes. Even under identical plasma conditions, the exact degradation mechanism will vary depending upon the antibiotic. Fang et al. observed that hydroxyl radicals dominated the degradation of levofloxacin, whereas ozone and peroxynitrite were the main reactive species in the removal of sulfadiazine [143]. Similar variations were seen in the removal of sulfadiazine, norfloxacin and tetracycline [136]. A completely different approach was proposed by Shen et al., who used a ceramic catalyst to enhance the degradation of a nitroimidazole antibiotic in a dielectric barrier discharge. The catalyst acted as a source of oxygen vacancies and helped to create additional reactive oxygen species and thereby enhance the antibiotic destruction in the plasma discharge [146]. Earlier studies [147] also reported effective degradation of ofloxacin and ciprofloxacin, with structural changes attributed to the hydroxyl radical and ozone, but further analyses revealed that ciprofloxacin degradants exhibited higher antimicrobial activity post-plasma treatment, revealing that biological activity can be retained in the degradants. As a remediation process, plasma process removal of antibiotics in complex wastewater effluents is possible. However, it is recommended that plasma processes encompass the degradant structure–activity relationships to ensure that biological activity is eliminated against non-target organisms, and that life cycle safety of antibiotic compounds is achieved [147].

5. Conclusions

Plasma continues to enable a wide variety of innovative approaches in modern medicine. This varies from simple adhesive layers to attach functional coatings to the

direct application of plasma onto damaged or infected tissue. As the technology matures, we are seeing a greater interaction between novel plasma science and traditional pharmaceutical interventions as researchers strive to use the unique properties of plasma to enhance existing interventional strategies and to overcome known issues. When combined with the application of new additive manufacturing techniques and the maturation of plasma medicine, the authors anticipate a growing interest in plasma science from within the medical community.

Author Contributions: F.O. was responsible for investigation, data curation and writing—original draft preparation. L.O. was responsible for Conceptualization, writing—review and editing and supervision. P.B. was responsible for writing—review and editing, supervision and project administration. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest: Fiona O'Neill and Liam O'Neill are employed by TheraDep Ltd., a company involved in the commercialization of plasma devices for medical applications. Paula Bourke declares no conflict of interest.

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