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SCIENTIFIC PERSPECTIVE

PLASMA PROCESSES AND POLYMERS

Plasma-treated liquids in medicine: Let's get chemical

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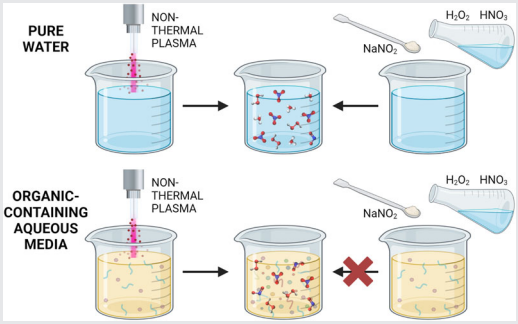
Abstract

Fundamental and applied research on plasma-treated liquids for biomedical applications was boosted in the last few years, dictated by their advantages with respect to direct treatments. However, often, the lack of consistent analysis at a molecular level of these liquids, and of the processes used to produce them, have raised doubts of their usefulness in the clinic. The aim of this article is to critically discuss some basic aspects related to the use of plasma-treated liquids in medicine, with a focus on their chemical composition. We analyze the main liquids used in the field, how they are affected by non-thermal plasmas, and the possibility to replicate them without plasma treatment.



KEYWORDS

chemical composition, cold plasma, plasma medicine, plasma treatment, plasma-treated liquids

Non-equilibrium plasma is used in a vast variety of biomedical applications, both in clinical and biomedical material/device processing and research environments.[1] The use of plasmas for treating living organisms can be carried out through two different approaches: *(i) direct*, when plasma is put in contact with, or remotely switched on the target, and *(ii) indirect*, in which the effect of the plasma is mediated by liquids (plasma-treated liquids, PTLs), hydrogels or gases (plasma-treated gases[2]).[3–5] The indirect approach in general, and the use of PTLs, has led to a huge advance in the biomedical field because it allows treating living cells and tissues with milder conditions than direct plasma and reaching internal tissues with

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injections or catheters without the need of surgery, resulting in a minimally invasive therapy for patients. These aspects have resulted in unprecedented possibilities in some specific applications, such as plasma-assisted tissue regeneration and the selective treatment of internal tumors with remarkable results.[6]

All of this made the study of PTLs and their composition extremely popular within the plasma medicine community. However, it is not uncommon to see works on this topic in which somewhat trivial findings are presented as novel discoveries and the action of plasma applied as PTL is overemphasized. This is at least partially due to the incomplete chemical analysis of PTLs and the unfortunate "tunnel vision," which results in studies often being too sectorial and application-focused, without a critical assessment of the induced chemistry. For this reason, in this paper, we want to discuss some important aspects related to the use of PTLs in plasma medicine with a special focus on their composition and the related reactivity. Part of the confusion that exists when talking about the chemistry of PTLs is reflected in the variety of different names that are continuously proposed to address them. Acronyms like plasma-activated liquid (PAL), plasma-supplemented liquid (PSL), plasma-conditioned liquid (PCL), plasma-processed liquid (PPL) can be found in literature and all mean the same thing. Each author uses the term they prefer, often without a clear reason behind the choice. This *de facto* limits and complicates unnecessarily any bibliographic research on the topic. Terms like "activated" and "conditioned" that are very popular within the non-thermal plasma community were proposed more than 15 years ago, when the chemical composition and reactivity of these liquids were still largely unknown. Moreover, "activated" implies that plasma treatment turns on some dormant properties of the liquid which is misleading and scientifically controversial. We suggest the use of "treated" or "processed" (less popular) that have similar meanings and simply indicate that a liquid has been treated by plasma.

In this paper, we focus exclusively on biomedically relevant PTLs all of which are aqueous, although plasma treatment of solutions in purely organic solvents is also done for applications in production of biomedical tools.[7]

The liquids that are used to produce PTLs are exposed to direct plasma and therefore—to all of the gaseous plasma components generated during the treatment. Primary plasma reactive oxygen and nitrogen chemical species (RONS), both short-lived and long-lived, can interact with the solution and with each other, yielding secondary RONS. Their nature and amount is tightly dependent on the experimental parameters of the plasma process, the chemical composition of the starting liquid, and the type of plasma source used.[8–10] The choice of each one of these parameters is able to address the formation of certain reactive species instead of others. Nonetheless, after the treatment, only the less reactive (long-lived) chemical species remain in solution and can then be exploited in different fields. For the sake of most non-thermal plasma applications, the distinction between short-lived and long-lived species can be set, according to their half-life time in water, around 10 s (Figure 1). In other words, all species that can be detected soon after the process and "used" after the treatment, can be considered long-lived; all species that do not last long enough in solution to be detected and quantified when the plasma is turned off are considered short-lived. From this definition, we exclude all the species "trapped" by chemical probes added before or during the plasma treatment. The most common short-lived RONS detected in aqueous solutions during a plasma treatment, in the presence of N_2/O_2 mixtures, are hydroxyl radical (HO), atomic oxygen (O), superoxide radical anion (O_2^-) and the related hydroperoxyl radical (HOO), singlet oxygen ($^1O_2$), ozone (O_3), nitrogen oxide and dioxide (NO, NO_2), and peroxynitrous acid (ONOOH) or its anion ($ONOO^-$). These species are very reactive and are the major effectors in the oxidation of inorganic or organic compounds in water solutions. They are not persistent in water, with half-life times that can range from 10^{-7} to 1 s.[4] They do not accumulate in solution during the plasma treatment, but reach a steady-state concentration, whose value depends on their reactivity. On the other side, long-lived species, like hydrogen peroxide (H_2O_2, formed from the primary HO), nitrite and nitrate ions (NO_2^- and NO_3^-, formed from the primary NO, NO_2, NO_3),[10] can be very stable, from days to months or even years, depending on the storage conditions and chemical composition of the

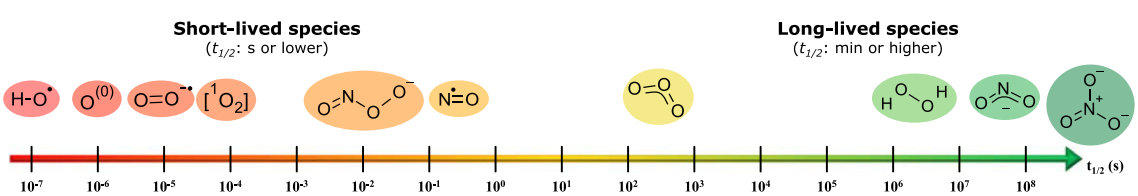

FIGURE 1 Main reactive oxygen and nitrogen species generated by non-thermal plasma treatment in liquid water. The lifetimes indicated are average values and can change per experiment.

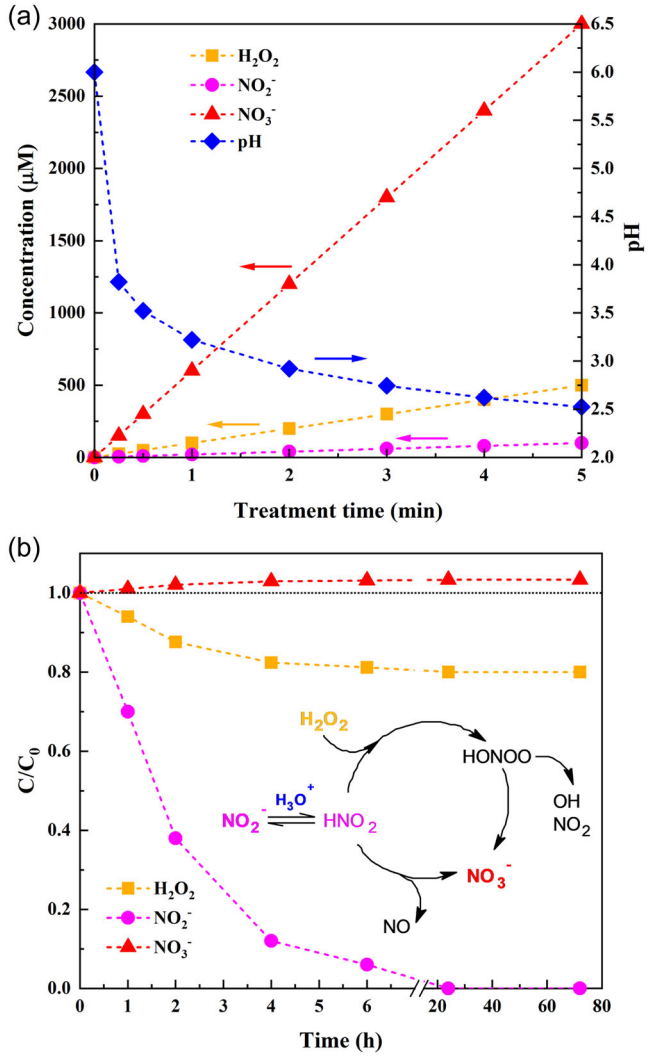

FIGURE 2 (a) Typical trend of long-lived reactive oxygen and nitrogen species (RONS) (H_2O_2, NO_2^-, and NO_3^-) in pure water during plasma treatment. (b) Typical trend of long-lived RONS in plasma-treated water with acidic pH. Inset: scheme showing the reactivity of long-lived RONS in water solution at acidic pH (<3.5). The pK_a of nitrous acid is 3.14 at 25°C. The data are adapted, with permission, from Labay et al.[14] Copyright © 2020, American Chemical Society.

starting liquid. These long-lived species can accumulate in solution during a plasma treatment and can be detected and quantified on an extended period of time after the plasma is turned off.

We acknowledge that some chemical species can be assigned to either group depending on the conditions (temperature, pH, etc.), such as NO, ONOOH/$ONOO^-$, and O_3. Although technically less reactive than, for example, radicals and $^1O_2$, they do not remain stable in liquid for extended periods of time, and therefore we consider them short-lived in this work. These species (H_2O_2, ONOOH, etc.) are formed in the gas and/or in the liquid phase depending on the experimental setup and conditions.[11,12]

As mentioned above, nearly all liquids used for biomedical applications are water-based and can be divided into three categories according to their chemical compositions: (i) pure water, (ii) aqueous solutions containing inorganic salts, and (iii) aqueous solutions containing organic matter. For clarity, we refer to deionized/distilled water as "pure" due to the maximally low presence of solutes. In practice, most of the solutions and media used in biology that contain organic matter, also contain inorganic salts. Hence, these three categories can be seen as a range of increasing chemical complexity. The effect of non-thermal plasma treatment on these liquids is mainly to induce certain chemical species within the liquid, and therefore the reactivity of the whole solution by opening chemical pathways that were not possible in the untreated liquids. Therefore, understanding the exact chemical composition of PTLs is fundamental for achieving a full control on biological effects to evaluate their use in clinics, including possible production of toxic substances. One of the main limitations is the detection and quantification of RONS in matrices like PTLs, challenged by potential inaccuracies and artifacts.[4,13] This aspect becomes more relevant as the chemical complexity of the starting liquid increases. We will briefly discuss these three groups of liquids and the effect of the plasma treatment on each of them.

Pure water is not an ideal medium for biomedical applications, due to its very low osmotic concentration, but it is studied in many cases, as it has a rather low chemical complexity. We note, however, that there are differences between composition (including the pH-related dissociative equilibrium) of pure/ideal and real distilled/deionized water. Plasma treatment of pure water results in the accumulation in solution of the main long-lived species: hydrogen peroxide, nitrous acid and nitric acid (Figure 2a, yellow, purple, and red dots). In most applications, the production of HNO_2 and HNO_3 and their dissociation in water, causes the pH of the solution to drop from 5.5 to 6.0 to typically 2.5–3.5, depending on the treatment conditions (Figure 2a, blue dots).

After the treatment, if the pH is sufficiently low (<3.0–3.5), the induced nitrite ions are partially protonated ($pK_a = 3.14$ at 25°C). HNO_2 is not stable in water and decomposes to give HNO_3 and NO, but in plasma-treated water (PTW) it can react with H_2O_2 to generate ONOOH that, in turn, can dissociate to HO and NO_2 or rearrange to HNO_3. All these reactions are reported in the inset of Figure 2b. The net effect of these reactions is the eventual conversion of nitrite ions to nitrate ions, and a reduction of the concentration of H_2O_2 (Figure 2b). These reactions occur on a time scale from several min to

several days, depending on the pH, and lead to a continuous generation of secondary radicals in solutions (NO, NO_2, and HO) which, as mentioned before, can reach low steady-state concentration in solution and can be detected indirectly.[15] In principle, when all of the nitrite moiety has reacted, the only persisting solutes are H_2O_2 and nitrate, which remain stable in water and no secondary RONS are generated through reactions in the liquid phase. Because the biological reactivity of NO_3^- is very limited, all biomedical effects of such PTW are therefore due to the accumulated H_2O_2. It must be noted that although another relevant plasma-produced RONS, peroxynitric acid HOONOO, can be induced in PTW, it is a very rare product and, to the best of our knowledge, has only been reported once.[16]

Aqueous solutions containing inorganic salts are more common in the biomedical field than pure water due to their osmolarity, similar to physiological liquids, and/or buffered pH. The most common are: saline solution (NaCl), Ringer's saline solution (NaCl, KCl, $CaCl_2$, $NaHCO_3$, and $MgCl_2$), phosphate buffers ($H_3PO_4/H_2PO_4^-/HPO_4^{2-}/PO_4^{3-}$), phosphate buffered saline (phosphate buffer with NaCl) and nondeionised tap water (variable composition). During the plasma treatment of these solutions, most of the reactions happening above and in the liquid phase are the same that were mentioned before for the treatment of pure water. Regarding long-lived species, the majority of the publications report the in-liquid accumulation of H_2O_2, NO_2^-, and NO_3^-. The most important difference is when the solutions are buffered at a neutral pH (6–8), a case that is very common in biomedical applications. In this case, the pH does not decrease as a function of the plasma treatment time. After the treatment, NO_2^- remain deprotonated, and their concentration does not decrease with time as it does at low pH. Consequently, all reactions reported in Figure 2b that generate secondary radicals or even peroxynitrous acid in water do not occur, and any effect of these PTLs on biological systems must be ascribed mainly to H_2O_2 and NO_2^-, alone or in combination. However, when saline solutions are treated by plasma it is important to consider that, among reactive species mentioned above, there are reactive chlorine species like hypochlorites ($HOCl/ClO^-$), chlorites (ClO_2^-), chlorates (ClO_3^-), and chlorine dioxide (ClO_2) induced in solution by the plasmas.[17] For example, ClO^- is a species with extremely strong biological effects, however, it must be noted that it is highly reactive with both H_2O_2 and NO_2^-.[18] Therefore, it can be stable in solutions only in the case of O-rich plasmas with high O atoms production[17,18] and limited H_2O_2 and NO_x. In buffers, phosphorous-based solutes are considered nonreactive in the PTL milieu,[19] and hypothetically, in-situ formation of other species such as carbonate radical anions should be also possible,[20] but not reported in PTLs.

Finally, solutions containing organic matter are also very common in biomedical applications. Most of the cell culture media, for example, contain sugars, amino acids, vitamins, and other organic acids. Some are supplemented with oligo-peptides and proteins. The chemical complexity of these solutions can be very high, according to the number of components, their structure and reactivity. In principle, non-thermal plasmas should be able to completely mineralize (complete oxidation to CO_2, H_2O, and inorganic salts) any kind of organic compounds, if a sufficient amount of oxidative RONS is provided, in a step-wise process.[21] Extensive characterizations by high-resolution mass spectrometry of PTLs containing different amino acids demonstrate the hydroxylation and nitration of aromatic rings, sulfonation and disulfide linkage in amino acids containing thiol groups like cysteine, sulfoxidation of organic molecules containing an S-methyl thioether side chain (e.g., methionine) and formation of amido-derivatives and ring-opening of five-membered rings (e.g., histidine and proline).[22] Other than amino acids, carbohydrates are involved as the primary energy source in cell culture media in the majority of in vitro studies. It was shown that, up to 90% of D-glucose could be converted into D-gluconic acid, D-glucuronic acid, gluconolactones and a number of minor products,[23] which all have biological effects by affecting the metabolytic cycles of living organisms.[24] Sodium lactate is another very common organic component of many cell culture media and solutions for infusion. It can be oxidized by direct plasma treatment to 2,3-dimethyl-tartaric acid or to pyruvate—a known scavenger of H_2O_2—thus affecting the long-term reactivity of the PTL.[25,26] Experiments performed in polysaccharides (alginate, methylcellulose) and proteins (albumin, gelatin, lysozyme, RNase, and superoxide dismutase) solutions showed that direct plasma treatment is able to fragment and to oxidize, to a different extent, the biopolymers, affecting their functionality, and generating intermediates with different reactivity.[14,27–30] Finally, a direct plasma treatment of biopolymer solutions leads to the enhancement of long-lived species (H_2O_2 and NO_2^-) in solution, likely proceeding through the generation of organic peroxides and/or by involving transient RONS like O and HO radicals.[29,31] Ultimately, organic-containing solutions may expectedly contain the most diverse range of biologically relevant species: organic biologically relevant molecules and the whole range of inorganic RONS as described for the two previous types of aqueous systems.

All the above-discussed chemical composition of PTLs bring us to one of the most typical question on the role of plasma that almost anyone working in the field has been asked: "Would it be possible to obtain solutions with the same composition and biological effects simply by mixing

together the individual components?" As expected, the answer is not binary. In the case of pure water and most buffered/saline solutions, the answer is "yes." Let us consider a "mock" solution obtained by dissolving, in water or buffers, certain amounts of H_2O_2, NO_2^- and NO_3^- (as e.g., potassium or sodium salts) and adjusting the pH with for example, HNO_3 or HCl—that is, fully mimicking all species and pH as would have been generated by plasma. Several studies have proven that such mock solutions have the same biological effects as the corresponding plasma-treated ones.[32–34] This evidence encounters the opposition of many researchers working in the field who defend the utility of using plasma to generate these liquids. This sort of inertia has many roots, and one of them is the lack of analysis of the chemical composition of PTLs. During the plasma treatment, the degree of complexity of the system is very high due to all the short-lived reactive species that are generated and/or transferred into the liquid phase, and which are responsible for a very large list of biomedical plasma effects—but solely during the direct plasma treatment.[35,36] Here, plasma is a unique chemical and biological tool, allowing production of short-lived species in a fairly simple manner. We also note that other agents of direct plasma treatment, such as UV radiation and electromagnetic field, were reported to play a role in the overall biomedical effect. In contrast, the only effects of PTLs are exclusively due to the chemical species, specifically the long-lived ones remaining in solution after the plasma treatment, when the plasma is turned off. As mentioned above, in buffers H_2O_2 and NO_2^- are the only agents. In pure water, if the pH of the solution decreased substantially during the treatment (Figure 2a), a continuous generation of the highly reactive peroxynitrite ions is possible (Figure 2b), until at least one of its precursors—H_2O_2 or HNO_2—is depleted. With saline media, in a somewhat rare case of plasma producing large concentrations of O atoms and low concentrations of virtually everything else, the only stable agent is ClO^-. Clinically speaking, this effectively renders PTW and organic-free PTLs meaningless. In a clinical setting, it is much simpler to employ commercial H_2O_2, nitrite salts, hypochlorite (as e.g., NaOCl salt) and HNO_3/HCl. These chemicals are very cheap (more energy-efficient production methods when compared with plasma[37,38]), readily available (large-scale production), and have very long shelf lives (sold as solids or in solution with stabilizers). Moreover, they can be mixed in a solution in any desired ratio, while tuning their production at a specific ratio by plasma is a big task on its own. Thus, if H_2O_2 or ClO^- are main agents, making their solutions from a stored chemical is much easier, cheaper, and more controllable than using plasma. If the effects are due to peroxynitrite formed under acidic conditions, then mixing H_2O_2, KNO_2 and HCl/HNO_3 (i) when desired and (ii) in concentrations desired, is much more feasible than plasma-generating a solution which cannot preserve its effects unless frozen.[39]

On the other hand, organics-rich solutions are a lot more complex, and at least part of the activity of such PTLs can be attributed to the secondary organic agents generated via reactions with the primary plasma RONS and to secondary RONS continuously generated by organic molecules in a concentration-dependent fashion.[31] These secondary RONS can prolong the effect of PTLs over time and decrease the aging of such solutions, without requiring additional stabilizers. The exact composition of such plasma-treated organic-rich solutions cannot be easily determined, and is therefore nearly impossible to substitute with a "mock" solution.

But this does not mean that the whole research on PTW is not useful or important, it depends on the application of the liquids. In the case of most medical applications, like for example, the injection of a water solution containing reactive species, into a patient to treat a tumor or to stimulate the regeneration of a tissue —then it is easier, faster, cheaper and more controllable to simply use commercial chemicals than to use plasma which would cause a lot of inconveniences, among which are issues with storage and reproducibility. Besides, the cost of electricity used to generate plasma makes the very concept unfeasible. In contrast, in a scenario in which such chemicals are not readily available, for example, due to transport or other issues, but renewable electricity is (e.g., via solar energy, in many developing countries), PTLs become a viable alternative. Finally, of course, the use of PTW is not limited to medicine. The immediate example is agriculture, where non-thermal plasma could be a valuable auxiliary technology to the otherwise unsustainable centralized industrial nitrogen fixation into PTW for fertilizers.[40,41] The use of PTW for nitrogen fixation here eliminates the issue of costly transportation and storage of potentially explosive chemicals such as NH_4NO_3.[41,42]

To summarize, we believe that PTLs in medicine have a great potential—taken with a pinch of salt: if commercial chemicals are cheaper and simpler in a specific clinical environment, but yields the same effects (e.g., pure water, or buffers), the use of plasma to generate PTLs is an unnecessary complication. On the other hand, plasma synthesis of molecules in liquids remains an intriguing topic of research where the dynamics are extremely complex, and there is still a lack of mechanistic understanding of the processes due to the plethora of components potentially involved.[43] Gaining insights into these processes could enable novel applications yet to be explored by the scientific community.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable—no new data generated.

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