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Research review paper

Nonthermal plasma — A tool for decontamination and disinfection

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ABSTRACT

By definition, the nonthermal plasma (NTP) is partially ionized gas where the energy is stored mostly in the free electrons and the overall temperature remains low. NTP is widely used for many years in various applications such as low-temperature plasma chemistry, removal of gaseous pollutants, in gas-discharge lamps or surface modification. However, during the last ten years, NTP usage expanded to new biological areas of application like plasma microorganisms' inactivation, ready-to-eat food preparation, biofilm degradation or in healthcare, where it seems to be important for the treatment of cancer cells and in the initiation of apoptosis, prion inactivation, prevention of nosocomial infections or in the therapy of infected wounds. These areas are presented and documented in this paper as a review of representative publications.

Contents

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1. Introduction

The consumers' increasing demand for increased food quality improvement focuses mainly on lower preservative and other chemical contents. The production of minimally processed, pre-packed, ready-to-eat fruits and vegetables or salads has also increased rapidly in recent years. Prevention of food-borne infections requires permanent care starting from the acquisition of raw food materials to food consumption by consumers. A number of methods limiting microbial contamination are used in food production, based on changing the properties of foods such as water content or pH, on diverse methods of heating and on the effect of various types of radiation or high pressure. These methods provide good results in a number of cases, however, sometimes they are expensive, there is a lack of effectiveness, or they are too slow. Some methods, moreover, adversely alter food properties such as color, taste and smell, or damage their structure. Other adverse effects sometimes occur, namely a decrease of the valuable nutritive content, or even the formation of toxic by-products. The disadvantages of the methods used so far initiated a search for new approaches.

The use of nonthermal plasma (NTP) may remove some of the shortcomings mentioned. NTP which was recently tested for microorganism inactivation, ready-to-eat food preparation, or biofilm degradation, seems to be an emerging antimicrobial technology predominantly for decontaminating of infected surfaces and potentially of volumes. In healthcare, plasma treatment was applied to cancer cells and in the initiation of apoptosis, prion and other biomolecule inactivation, prevention of nosocomial infections or the therapy of infected wounds. Among the new methods for the inactivation of the undesirable micro-flora, NTP provides a sufficient effectiveness accompanied by minimized damage of exposed biomaterial, such as plant and animal tissues, and processed foods or thermo-sensitive packaging materials. So far, it appears that at least in some cases, the minimal damage of antioxidants in food and the minimized content of residues of the substances with disinfectant effect introduced into food may be expected after plasma treatment. This paper concurs the six year old review of Moreau et al. (2008), published in this journal. Since the publication of the manuscript, a number of papers have appeared including review papers in the areas of plasma decontamination (e.g., De Geyter and Morent, 2012; Misra et al., 2011; Ehlbeck et al., 2011), plasma and food system interactions (e.g., Surowsky et al., 2014b; Pankaj et al., 2014) and plasma medicine (e.g., Kong et al., 2009; Morfill et al., 2009). Recent publications also include books (Laroussi et al., 2012; Fridman and Friedman, 2013) and compendia based on congress proceedings (Hensel et al., 2012). However, the recent review summarizing and pointing out the practical applications of NTP for the food industry and biotechnology is missing. This work presents a short introduction to NTP and a review of representative publications documenting the food industry practically oriented point of view. We conclude, that this review will be the source of both the inspiration and useful information for decontamination and disinfection advances in biotechnology and also in the rapidly developing field of plasma medicine.

1.1. Plasma and its generation

Plasma is a partially or fully-ionized gas. Generally there are two types of plasma recognized, thermal and nonthermal plasma. For more details see the classical books by Loeb (1960) and Raether (1964), or the more contemporary book by Fridman and Kennedy (2004). A nice introduction into plasma physics and plasma generation is also in the book devoted to plasma medicine (Laroussi et al., 2012), or in a review paper (Tendero et al., 2006). In thermal plasma, the electrons are at nearly the same temperature as heavy particles (ions, neutral molecules and atoms), the plasma is in a local equilibrium state and its temperature reaches the values of several thousands of Kelvins. In contrast, nonthermal plasma (NTP) can be generated if most of the coupled energy is transmitted into the electrons and only their temperature reaches the high values; plenty of various plasma-chemical reactions are induced. In this case, the neutral particles and ions bear only negligible energy and stay cold. The low macroscopic temperature is the main feature of NTP and enables the treatment of thermolabile materials. NTP can be generated by electrical discharges in gases under either low or atmospheric pressure.

The discharges burning at atmospheric pressure are mostly used in presented areas, because the costly vacuum techniques are absent and the manipulation with treated object is, therefore, easier. The discharges burn most often in the atmosphere of natural or synthetic air, nitrogen, oxygen, helium, hydrogen, argon or their admixtures. Other types of atmosphere are used only rarely. NTP generated at atmospheric pressure consists of various active agents, namely UV photons, and particles as neutral or excited atoms and molecules, negative and positive ions, free radicals and free electrons. In commonly used sources, the majority of reactive species are the following:

- electronically and vibrationally excited oxygen O_2 and nitrogen N_2,
- active form of oxygen molecules and atoms (reactive oxygen species, ROS) such as atomic oxygen O, singlet oxygen $^1O_2$, superoxide anion O_2^- and ozone O_3,
- reactive nitrogen species (RNS) such as atomic nitrogen N, excited nitrogen $N_2(A)$, nitric oxide NO•,
- if humidity is present H_2O^+, OH^- anion, OH• radical or hydrogen peroxide (H_2O_2) is also generated.

However, the composition and abundance of these agents vary substantially with the type of plasma source. Moreover, it is very hard to understand the real interaction of plasma agents with the material applied on, for details see e.g., Yousfi et al. (2010, 2011). Recent extensive reviews (Graves, 2012; Kelly and Turner, 2013) describe several opinions of the plasma reactive nitrogen and oxygen species interaction with biomaterials, the physiologic processes and the possible therapeutic responses. The common electrical discharges used to generate nonthermal plasma are the corona discharge, the dielectric barrier discharge, the microwave discharge, and a special arrangement called plasma jet. A detailed description can be found in a book by Raizer (1991), in the first chapters of Laroussi et al. (2012), or in a review paper by Tendero et al. (2006). To see how the discharges look, three discharge types are schematically depicted in Fig. 1.

1.1.1. Corona discharge

Corona discharge is usually generated on sharp electrodes, such as tips, pitpoints, or thin wires, with imposed high voltage. The electric field of high intensities is formed close to such points and the active region of corona and plasma generation occurs. In recent years there are also frequently tested modified forms of corona-based discharges, e.g., transient spark.

1.1.2. Dielectric barrier discharge (DBD)

Dielectric barrier discharge (DBD) is alternating current generated discharge burning between two electrodes separated by a solid dielectric material (glass, plastic). The dielectric avoids the charge transport (i.e., current) and the discharge burns due to the electric induction

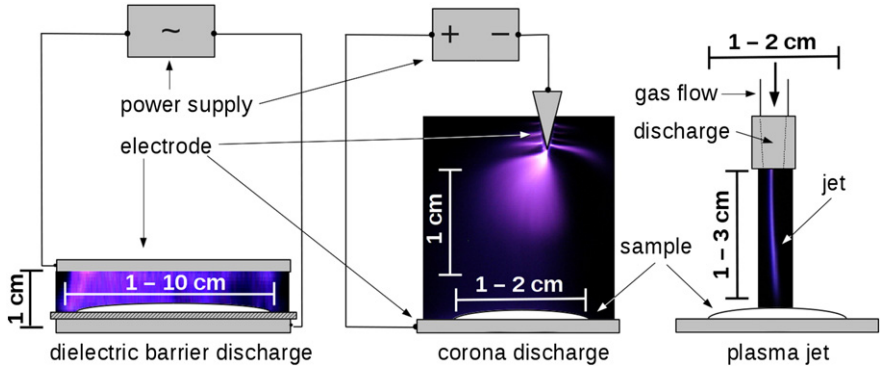

Fig. 1. Schematical depiction of three typical electrical discharges for generating the NTP with typical sizes indicated and discharge appearance.

and the polarization of dielectric only. While the corona discharge active region appears only close to the point electrode, or is limited up to units of mm, the DBD electrodes are typically metal plates and therefore the plasma area is in an order of magnitude larger and limited by the power of high voltage supply only.

1.1.3. Microwave discharges (MD)

Microwave discharges (MD) are generated by electromagnetic waves with frequencies exceeding hundreds of MHz. The discharge typically burns in a box, where the waves are in resonance. Due to the necessity for a microwave generating apparatus and the need for shielding, this type, in general, seems to be of lesser importance in biotechnology, but was often used in the basic research of NTP interactions with biomaterials. However, MD present a very progressive source in the plasma jet configuration, where it belongs to one of the few NTP plasma sources already certified for medical use (Isbary et al., 2013).

1.1.4. Gliding arc

Gliding arc is a typical source of thermal plasma, but in some conditions it may also produce NTP. This discharge typically burns between two diverging electrodes blown by injected gas. The discharge initiated in the narrowest inter-electrode area is wafted by flowing gas outside the diverging area. The gliding arc combines the advantages of thermal and nonthermal plasma, i.e., nonthermal plasma conditions at a higher power.

1.1.5. Plasma jet

Plasma jet is not so much strictly a "type" of discharge than a special configuration of previously described discharges. Generally, the active region of used discharge is blown by flowing auxiliary gas, which pulls the particles outside the electrode area in propagating ionization waves and forms a stream of active particles burning as a small jet. Local applicability and higher power are coupled and abundantly used in types of plasma sources called jet, plasma pen, plasma torch or plasma needle.

Because of the simple design and easy maintenance, for practical usage, most discharges are operated at atmospheric pressure. There are works studying the microbicidal properties of plasma generated even at low pressure (e.g., surfatron discharge, Straňák et al., 2006), however, this direction of research seems to be of lesser importance. Nevertheless, many commercial sterilizers working at a reduced pressure and/or in the atmosphere of additional disinfecting agents (hydrogen peroxide, peracetic acid) were introduced to the market. Among them, various models of Sterrad® series (Johnson & Johnson Co.), Plazlyte™ (AbTox Inc., Mundelein, IL) or PE-200 (Plasma Etch Inc., Carson City, NE) should be mentioned. These equipments appeared to be a suitable substitute for high temperature autoclaves and low temperature sterilizers based on action of toxic ethylene oxide, but all of them were intended for sterilization of temperature or corrosion susceptible instruments as endoscopes, the biotechnological applications are negligible. Pertinent evaluations were presented by Bryce et al. (1997), Franchini et al. (1997) and Adler et al. (1998). Here, mainly the results from discharges burning at atmospheric pressure with high potential for application in biotechnology are described.

2. Plasma decontamination

Microbial decontamination is considered as the decomposition or removal of microorganisms, i.e., viruses, bacteria and fungi; prions are also included. The European standard EN 12740 recognizes all biological agents causing infection, allergy or intoxication as microorganisms. In addition, viroids, plasmids and plant and animal cells are also included. Microbicidal treatment is defined as an attempt to destroy microbes; this term is a collective for sterilization, disinfection, as well as aseptic and antiseptic procedures.

The method of exposure may be direct, where the sample is in direct contact with the plasma, or semidirect, where the sample is placed out of reach of shortliving reactive species. In basic research indirect exposure may also be interesting, where the discharge is closed in a transparent chamber, so the effect is caused by irradiation only. The microbicidal effect may be also "saved" in a medium, e.g., plasma activated water (see later).

2.1. Bacterial inactivation

Among the early experiments devoted to interaction of discharges with bacteria, the paper of Mizuno and Hori (1988) should be mentioned, who applied pulsed high voltage on suspensions of *Saccharomyces cerevisiae* and *Bacillus natto*. Nevertheless, the paper of Mounir Laroussi (1996) should be considered as the truly first application of nonthermal plasma (NTP) as a powerful sterilization agent. An apparatus which can routinely generate a glow discharge at atmospheric pressure and in a uniform steady-state was developed at the Plasma Science Laboratory of the University of Tennessee and used for microbiological treatment. The YEPG medium contaminated by *Pseudomonas fluorescens* bacteria was treated by plasma discharge for 10, 15 and 20 min. It was found that all samples were completely sterilized without damaging the medium itself. Since then, many articles have been written and many investigations have been made in order to answer some questions: what is the most effective plasma regime?; which minimal plasma power density is sufficient for killing of microorganisms?; what kind of physical processes is mostly responsible for sterilization?; what processes, biological and chemical, induce cell death?; which type of gas is more desirable for a particular application? Some of these questions were more or less appropriately answered.

We are not able to quote all original articles. Fortunately, several topical reviews have been published, in which the most important things are concluded. The first review on NTP based sterilization was presented by Moisan et al. (2001). It is focused on the characterization of the inactivation process studied on various bacteria as the

inactivation kinetics using D-values and survival curves (survival colony forming units (CFU) versus treatment time). The study compared several bacterial species (*Escherichia coli*, *Staphylococcus aureus*, *Bacillus subtilis* spores) under different discharges (DBD, MW discharge) and different gases (air, pure argon, O_2, CO_2, and mixtures N_2/O_2, Ar/O_2).

Beside the fundamental review (Laroussi, 2005), further papers and reviews of Laroussi (2003, 2008, 2009) and Laroussi et al. (2000, 2006) represent a very useful tool for orientation in the early years of plasma applications in bacterial inactivation and in medicine overall.

The work of Ehlbeck et al. (2011) focused on microbiological verification of plasma efficiency. Approximately 20 types of microorganisms (Gram-positive and Gram-negative aerobic and anaerobic bacteria, viruses and yeasts) are compared in this review to ensure process efficiency. In the well-arranged table, the assortment of inactivation results achieved with different NTP sources (corona discharges, DBD, plasma jet, MW discharge) is summarized. Additional information, such as reduction factor, exposure times, gas, and initial number of CFU, microorganism's environment and particular experimental conditions are also given. Depending on the conditions low temperature plasma treatment can inactivate (kill) the microorganisms and significantly decrease (up to 5–7 magnitude) the number of CFU in suspensions or on surfaces within 10–1800 s.

Another review of Fernández and Thompson (2012) is focused on the sensitivity and resistance of different *Salmonella* serovars on different surfaces or in different suspensions. This study is important for applications of this technique in the food industry to keep the microbial safety of fresh products. Various microorganisms were tested, as well as various plasma sources working at various parameters were used, resulting in variable composition of microbicidal agents. In combination with the complex microbial test methods using different procedures, presented in the review, it leads to an inhomogeneous characterization and makes the results incomparable. For the comparison, the works used only one plasma source and methodologies applied on various microorganisms are more suitable. Scholtz et al. (2010) determined the sensitivity of nine microbial species, including Gram-positive and Gram-negative bacteria, *Deinococcus radiodurans* and *Geobacillus stearothermophilus* spores and the *Candida albicans* yeast. The sensitivity of bacterial vegetative forms of all bacteria was comparable, whereas inactivation of *Candida* and *Geobacillus* spores needed longer times of exposure. Lee et al. (2006) reported the comparison of the sensitivity of *E. coli* and *S. aureus* as vegetative bacteria, spores of *B. subtilis* and *S. cerevisiae* yeast to the He/O_2 plasma jet on dry surfaces. While the inactivation of vegetative bacteria occurred within approximately 1 min of exposure and of yeast in several minutes, the inactivation of bacterial spores decreased in 1 h of one magnitude only. In the case of water suspension decontamination, Scholtz et al. (2011) reported also a similar sensitivity of four vegetative bacterial species to the corona discharge inactivation where the inactivation occurred up to 1 min of exposure. However, the sensitivity of yeast is several times lower and occurs so far after 6 min. In general, however, it may be concluded, that the sensitivity of vegetative forms of planktonic bacteria varies somewhat across species. These differences are obviously lesser that those between vegetative bacteria and spores, between planktonic and biofilm forms, or between bacteria and fungi. As a rule, the secondly mentioned forms need much longer exposure times to inactivate than those of bacteria. A detailed comparison of sensitivity of particular bacterial strains, however, is difficult because it is significantly influenced by the nature of plasma source and other experimental parameters of plasma.

Other works have studied the inactivation mechanisms, which are still not clear and are the aim of recent studies. For example, in Moisan et al. (2001), the inactivation of *B. subtilis* spores by N_2/O_2 NTP showed that the survival curve exhibits three inactivation phases. The authors claimed that UV radiation is responsible for the first phase due to the action on isolated spores, which may be also on the first layer of stacked spores. The slow erosion process by the active species is presumed to be responsible for the second phase, which is the slowest. Finally, during the third phase, UV hits the genetic material of the still living spores after clearing spores and debris. These phases appeared to be a function of exposure time and corresponded to changes in the kinetics of the inactivation process. The following works of Laroussi (2005), Machala et al. (2010), and others, however, have shown that the role of UV radiation is not the dominant microbicidal agent. On the other hand, Pavlovich et al. (2013) compared the effect of separated UVA and plasma treatment with both treatments in combination, and stated, that UVA and plasma produce a synergistic antimicrobial effect. In the work of Laroussi (2005), the evaluation of the inactivation kinetics is included and the role of various plasma components is discussed. Dobrynin et al. (2011) have studied the role of humidity and ions in various gas mixtures and have concluded that the presence of oxygen and water plays a crucial role for the generation of ROS and the inactivation efficiency. Hence, the role of microbicidal agents and the particular mechanisms of inactivation are still not clear and are under study. A detailed discussion of the mechanisms is beyond of the scope of this work and can be found in recent extensive reviews (Graves, 2012; Yousfi et al., 2014), where the relative contribution of compounds produced by NTP in air is analyzed and many intracellular biochemical reactions, biochemical pathways, where the RNS and ROS play important roles either in a positive or negative sense, are discussed.

2.2. Fungi inactivation

Filamentous fungi are ubiquitous in nature, but present a potential threat not only for humans, especially those who are immunocompromised, but also for economically important plants and animals. Although many fungi are common constituents of skin microflora, they can cause diseases under certain conditions. For inactivation of fungi various sterilization tools are available, as heat, chemicals or radiation, but their effect and efficacy are variable and often unsatisfactory and are sometimes accompanied by undesirable side effects. Compared to bacteria, the reaction of filamentous fungi with NTP has not been frequently examined. Therefore, there is no overview article concerning plasma decontamination.

NTP seems to have the potential for fungi inactivation in terms of environmental safety and human health. The first detailed study of the NTP surface decontamination of the filamentous fungi *Aspergillus niger* and the yeast *Candida lipolytica* was published by Akishev et al. (2008b): *Aspergillus* spores or *Candida* cells were spread on an agar medium surface and exposed to the atmospheric pressure plasma jet with variable gas mixtures (N_2+O_2). Inhibition zones of 30–40 mm in diameter were observed after 30–60 s of exposure.

The corona discharge inactivation of filamentous fungi (*Aspergillus oryzae*, *Cladosporium sphaerospermum* and *Penicillium crustosum*) and yeast (*C. albicans*) in water suspension was studied and compared with bacteria (*E. coli* and *Staphylococcus epidermidis*) by Soušková et al. (2011, 2012). While no significant differences in susceptibility was observed among bacteria (total inactivation occurred after 2–4 min of exposure), the susceptibility of fungi depends on the species. The total inhibition of spores in water suspension at an initial concentration of more than 10^4 CFU/ml occurred after 20–30 min of exposure of *Cladosporium* and *Penicillium*. For *Aspergillus*, only the decrease from the initial 10^5 CFU/ml to 10^2 CFU/ml was observed after 30 min of exposure. The full inhibition of *C. albicans* yeast occurred after 6 min of exposure. Moreover, in these works different growth rates were observed for exposed fungal spores and for the unexposed ones. The rate of micromycete growth exposed to a sublethal dose of plasma was visibly slower than that of the unexposed ones, the appearance of first colonies of exposed spores was delayed by 35–65 h.

The two following articles are devoted to the fungal species involved in common dermatomycoses like tinea pedis,skin and nail infections. The paper of Daeschlein et al. (2011) discusses the inactivation by a NTP plasma jet of clinical isolates of *Trichophyton rubrum*, *Trichophyton*

interdigitale, *Microsporum canis* and *C. albicans*. The decontamination of environmental infective material (shoes, dandruffs) and inhibition zones of fungal spores spread on agar surfaces were also described. In vitro, plasma irradiation was able to kill over than 90% of fungal spores within 30 s. Reproductive fungal elements were also inactivated by plasma ex vivo, namely in dandruff and in shoes. The paper of Švarcová et al. (2014) describes the NTP application for the treatment of a clinical case of human dermatomycosis. The mycosis caused by *T. interdigitale* was exposed to NTP for 10 min every day on one half of the lesion. The suppression of subjective discomfort was observed on the treated half after 8 to 10 days of treatment, whereas on the control half it persisted for more than 20 days. The presence of the etiological agent was lowered markedly during the initial stages and disappeared completely before 19 days of treatment. The Spontaneous healing occurred, but markedly later that in treated area.

There are several other articles and conference contributions dealing with inactivation of fungal spores. In Ghomi et al. (2012) the inactivation of some other fungal species, e.g., *Aspergillus fumigatus* using dielectric barrier discharge is demonstrated. In Na et al. (2013) the inactivation of *Fusarium graminearum*, *Fusarium oxysporum* and *Neurospora crassa* using MW plasma jet with various rates of gases such as nitrogen, argon and air is demonstrated.

The letter of Park et al. (2012) presents the cellular and molecular responses of the filamentous fungus *N. crassa* to the action of NTP produced by an argon plasma jet at ambient atmospheric pressure. *N. crassa* has been frequently studied as a model organism for human, animal and other pathogenic fungi. It was demonstrated, that the plasma application to water containing fungal spores caused significant cell death, affected spore germination characteristics, caused changes in the cell morphology (spores appeared to shrink and exhibited damaged membrane and destruction of cytoskeletal structures after exposure to plasma), and a reduction of the intracellular genomic content. It was revealed that transcription factor *tah-3* (i.e., one of the DNA-binding proteins responsible for the control of gene expression) might be one of the essential regulators allowing *N. crassa* tolerance to plasma exposure. Transcription factors are DNA-binding proteins that control the expression of genes involved in the regulation of life processes. This study together with Soušková et al. (2011, 2012) may also confirm the hypotheses, that fungi, and also all eukaryotic cells, are likely to have molecular mechanisms for tolerance to plasma stress. This phenomenon has been only recently described and there are not many authors engaged in similar studies. The hypothesis in question is quite unique so it is not yet possible to ground it on other articles. The phenomenon is yet to be thoroughly scrutinized.

A practical utilization of fungal treatment with plasma has been studied by Filatova et al. (2012). It was shown that pre-sowing treatment of seeds (crops and legumes) with plasma and radio-waves enhanced their germination and improved plant productivity probably owing to the stimulative and fungicidal effects.

In Čeřovský et al. (2013) the synergy effect of corona discharge burning in atmosphere of nebulized hydrogen peroxide was demonstrated. This combination was proved to be much more effective than that particular treatment by plasma or by nebulized hydrogen peroxide only.

General conclusions from all articles dealing with filamentous fungi may be summarized as follows: The fungicidal effect of plasma inactivation is weaker than the bactericidal effect under comparable conditions. Moreover, various fungal species display substantially different response; this holds also for different experimental plasma conditions and plasma sources. The different sensitivity of various fungi is apparent for yeast and filamentous fungi inactivation: The complete inactivation of bacteria is usually achieved after 2–4 min of exposure, whereas the inactivation of fungi occurred after 20–30 min, depending on fungal species, and after 6 min for yeast. This statement is valid for corona discharges (positive and negative), but generally speaking, the efficiency of inactivation is particularly dependant on the plasma source and its operating conditions. Varied intervals of inactivation in between bacteria and fungi might be obviously caused by differences in structure and composition of prokaryotic and eukaryotic microbes. The cell structure of fungi is more sophisticated than bacterial one. Thus, different plasma conditions must be adopted to achieve a comparable inactivation effect.

2.3. Virus inactivation

The lethal effect of plasma on viruses was demonstrated, e.g., by Venezia et al. (2008) and Yasuda et al. (2010) who consistently described activity of nonthermal plasma on DNA viruses. Also Alshraiedeh et al. (2013) demonstrated the atmospheric pressure NTP as a rapid and effective method for disinfection and cleaning of contaminated surfaces from nonenveloped viruses. MS2 bacteriophages and human enteric viruses were studied, among them the norovirus is the most common etiological agent of infectious diarrhea worldwide. Terrier et al. (2009) decontaminated the nebulized suspensions of respiratory viruses (respiratory syncytial virus, human influenza virus type A and parainfluenza virus type 3) of approximately 5 log(10) TCID 50/mL.

2.4. Inactivation of biomolecules

NTP also influences biomolecules by inducing their chemical or structural changes, which leads to the decrease of their enzymatic activity, functional changes or total degradation of the molecules. This influence was studied mainly on lipids, lipopolysaccharides, bovine serum albumin or prions. On the contrary to other works, the studies devoted to biomolecule treatment were focused mainly on the usage of NTP at low pressures of 10 to 100 Pa.

The interaction of O_2 inductive RF NTP with soybean lipoxygenase (SLO) and bovine serum albumin (BSA) at low pressures of ca. 100 Pa was described by Mogul et al. (2003). The treatment caused a lowering of BSA volume and SLO enzymatic activity. The work of Rossi et al. (2006) describes a MW discharge at low pressure (13 and 133 Pa) in an O_2/H_2 (50:50) atmosphere, used for the etching of lipid A from lipopolysaccharides. Lipid A bioactivity, expressed as interleukin IL-1b release, decreased by treatment with plasma to ca. 2 orders of magnitude within 5 min. The etching rate of lipid A increases with the increase of percentage amount H_2 in mixture and is approximately 8-times greater in an O_2:H_2 atmosphere as compared with Ar:H_2. Another work of Whittaker et al. (2004) studied the possibility of cleaning of surgical instruments from protein residues. Using energy-dispersive X-ray analysis and scanning electron microscopy they demonstrated, that strongly adherent protein residues on metallic surfaces of surgical instruments were not completely removed by the typical decontamination and sterilization procedure applied in hospitals. However, those residues could be removed using the plasma unit Plasma Etch PE-200 working at a pressure lower than ca. 100 Pa, which is a versatile commercial instrument designed for plasma removal of photoresistive materials. On the other hand, in Deng et al. (2007) the He/O_2 plasma jet was used for destruction of BSA proteins deposited on stainless-steel surfaces and it was shown that, in the case of incomplete protein removal, the treated protein sustained considerable degradation. Therefore, even when plasma treatment cannot completely remove all proteinaceous matters from surfaces, the residual proteins are likely to have a compromised integrity and perhaps a reduced activity, thus possessing lesser risk than that of untreated proteins. Moreover, it was shown that the maximal protein reduction of 4.5 logs occurred in 5 min, depending on the method of delivery and the amount of oxygen admixture in the background helium gas. In Kylián et al. (2009) the low pressure ICP was applied on selected homopolypeptides containing amino acids (poly(L-histidine), poly(L-lysine) and poly(L-arginine)). The most important conclusion is that the efficiency of degradation depends on the composition of the plasma discharges only and is almost independent of the chemical composition of the treated substrates.

Hence, it may be presumed that different proteins with different amino acids composition and sequences will be removed with similar rates. It also confirms the mechanism suggesting the dominant role of chemical sputtering in the removal of biological impurities from surfaces. The work of Von Keudell et al. (2010), using MW plasma at low pressure, has likewise shown that bioactivity of some biomolecules (LPS, lipid A, BSA and prions), namely pyrogens, can be greatly reduced even without completely removing them from the surface. In Takai et al. (2012), the He plasma jet was applied on lysozyme proteins in aqueous solution and decreases in enzymatic activity and changes of the secondary structure were observed. Recent work of Bartis et al. (2014) studied the deactivation of lipopolysaccharide (O111:B4) by Ar and H_2 MW discharge under low-pressure. Despite the negligible material removal, the radicals presented in H_2 plasma were demonstrated, which remove C – O and O – C═O bonds and cause oxygen depletion; this does not occur in the atmosphere of Ar.

The treatment of prions, the cellular membrane-bound glycoproteins, represents a special item in biomolecule removal schedule. In the prevalent α-helix conformation called PrP^C, prions are the common proteinaceous constituents of cell membranes. However, if their conformation changes into the β-sheet called PrP^{TSE}, they cause transmissible spongiform encephalopathies, incurable and lethal neurodegenerative diseases, referred to as bovine spongiform encephalopathy (BSE), Creutzfeldt–Jakob disease and others. PrP^{TSE} are protease-resistant, are not destroyed by many sterilization procedures, and represent a serious problem in veterinary and human medicine. Baxter et al. (2005) demonstrated the possibility of prion protein elimination by the action of Ar/O_2 plasma. A suspension of prions was bound to spheres of stainless-steel and deactivated with various agents including NTP. The degree of prion inactivation was determined by implantation of treated spheres into peritoneum of hamsters and following their survival. Whereas the prion inactivation by autoclaving was only partial, the plasma treatment ensured a complete prion inactivation. In the previously mentioned work of Von Keudell et al. (2010), the effectiveness of low pressure MW discharge NTP in inactivation of prions which adhered on the surface of steel wires or silk sutures was also reported. The work of Julák et al. (2011) reported a significant decrease of infectious prion particle concentrations after the corona discharge action. The point to plane negative corona in open air at ambient atmospheric pressure was used as the plasma source, the concentration of prions was measured as the CAD5 cell infectivity.

2.5. Biofilm destruction

Biofilms are structured communities of microorganisms engulfed by an extracellular self-produced polymer matrix and attached to biological or nonbiological surfaces (Costerton et al., 1999). The definition of biofilm evolved over the last 30 years, see Donlan and Costerton (2002). They defined biofilm as "… microbially derived sessile community characterized by cells that are irreversibly attached to a substratum or interface or to each other, are embedded in a matrix of extracellular polymeric substances that they have produced, and exhibit an altered phenotype with respect to growth rate and gene transcription." In their extensive review devoted to biofilms formed by clinically relevant microorganisms they enumerate many methods for biofilm intervention. Nevertheless, a remark concerning a possible action of NTP on biofilm is missing despite the fact, that Denes et al. (2001) previously described cold plasma deposition on mixed biofilm composed from Gram-negative bacteria *P. fluorescens*, *Salmonella typhimurium* and Gram-positive *S. epidermidis*. In their conclusion it was stated, that plasma approach may be applied in depositing antifouling covers on various materials used in food-processing equipments, and on medical implantates and other devices, e.g., catheters. Triandafillu et al. (2003) reported an in vitro study focused on adhesion of clinically isolated *Pseudomonas aeruginosa* strains on polyvinylchloride used for endotracheal tubings: after preliminary treatment of PVC with oxygen glow discharge plasma, the number of adhered bacteria was reduced.

The next study dealing with atmospheric plasma effect on biofilm forming bacteria, was published by Vleugels et al. (2005): the atmospheric $He:O_2$ plasmas appeared to be effective inactivation agents, capable of preventing unacceptable levels of discoloration of bell pepper (*Capsicum annuum*), caused by the biofilm-forming bacteria *Pantoea agglomerans*.

Abramzon et al. (2006) compared the effect of NTP and UV on planktonic and biofilm living microorganisms. They exposed the four day old biofilm of *Chromobacterium violaceum* to plasma for various times and found that 10 min of plasma treatment killed almost 100 % of the cells. This indicated that plasma treatment may be a potent way of biofilm removal. Further works published in 2008 by Vandervoort et al. (2008) and by Joaquin et al. (2009), supported the idea that the process of plasma action on bacterial cells occurs in double stages. In a first step cells lose viability and enter a viable but not cultivable (VBNC) stage. In a second step, they are actually killed. The study of Jiang et al. (2009) is also remarkable, where plasma is used for disinfection of human root dental canal colonized with oral bacteria derived from saliva biofilms, namely *Bacillus atrophaeus*. Cooper et al. (2010) found a similar effect, i.e., induction of VBNC forms of *Bacillus stratosphericus* after dielectric barrier discharge plasma treatment. Biofilm formed by oral cavity inhabitant *Porphyromonas gingivalis* was treated by cold plasma Xiong et al. (2011). Cells in a 15 μm thick biofilm were deactivated, but they did not lose their structure.

An extensive report of Ermolaeva et al. (2011) presents the study of the effect of NTP torch on Gram-negative and Gram-positive bacteria in biofilms. The obtained results proved the susceptibility of both types growing in biofilms to the argon plasma. Nevertheless, the effectivity of decontamination decreased from the bacterial layer to its base, therefore it depends on the biofilm thickness. Pei et al. (2012) applied NTP plasma jet on biofilm of *Enterococcus faecalis* and visualized the lethal effect by confocal laser scanning microscopy (CSLM). According their data, the cells from the bottom layer of a biofilm 25.5 μm thick were devitalized after a 5 min long treatment by NTP.

Destruction of *Candida* biofilm by NTP was studied by Sun et al. (2012) using $He:O_2$ (2%) plasma alone or in combination with generic antifungal drugs; both treatments were able to inactivate *Candida* biofilms rapidly. One of the underlying mechanisms of plasma fungicidal activity, is generation of ROS. Brelles-Marino (2012) discussed the challenges of novel antimicrobial technology represented by NTP, and compared its impact on oral health as well as in fresh food with conventional sterilization methods. The technology is clean and reported to be safe both for the patient and the operator. Mai-Prochnow et al. (2014) reviewed recent advances in eradication of bacteria including biofilm-forming bacteria using plasma generated at atmospheric pressure. They conclude that much longer treatment times are needed for the complete eradication of biofilm than for killing of planktonic forms of the same species. Recently, Masák et al. (2014) evaluated possibilities of *Pseudomonas* biofilm removal. Among the eradication tools of biofilm they suggested that the treatment by oxygen glow discharge plasma modifies the polymer surfaces and prevents attachment of cells. Among papers devoted to dental applications, Kovalóvá et al. (2014) presented an ex vivo study dealing with biofilm formed by oral streptococci on the surface of extracted human teeth exposed to the NTP action; the effect of NTP on the treated surface enamel a dentine of extracted teeth was also studied. The results showed that NTP can reduce the number of such bacteria after 10 min of exposure by up to 3 logs. The same effect, within 5 min, was achieved using additional water electrostatic spraying into the discharge to the treated tooth surface. After plasma exposure, no significant alterations of the tooth surface, i.e., the composition and structure of the dental enamel or dentine, were observed neither by infrared spectroscopy nor by scanning electron microscopy. Matthes et al. (2013) applied NTP produced by a plasma jet on *S. epidermidis* and *P. aeruginosa* in in vitro biofilms. The plasma

treatment displayed led to a marked antimicrobial effect, at least as effective as the treatment with common antiseptic chlorhexidine digluconate, or even better. Niemira et al. (2014) tested plasma jet NTP for inactivation of *Salmonella* biofilms of several day old cultures. In the 15 s exposed biofilm, a reduction of 2 log 10 was observed as almost independent of culture age.

The technology is still somehow expensive compared to other sterilization methods. Anyway, cold atmospheric pressure plasmas represent an attractive alternative to traditional biofilm removal/detachment techniques.

2.6. Plasma activated water

After the treatment of pure water by NTP, an interesting phenomenon was observed by various authors, called plasma activated water (PAW) or water of dead; the bizarre term plasma acid also appeared. Briefly, it consists of persistence of microbicidal effect in the previously exposed water for a long time after the treatment. The direct action of plasma is believed to be mediated by various reactive particles; however, their lifetime is generally very short, so that the microbicidal effect persisting for a long time must be mediated by stable particles. Among them, the presence of nitrogen oxides NO_x and corresponding acids, hydrogen peroxide H_2O_2 and ozone O_3 was proved in exposed water or in phosphate-buffered saline.

To produce reactive particles, Ikawa et al. (2010) used the plasma jet in a helium stream or in helium and air stream in a closed system. A distinctive inactivation of *E. coli* and acidophilic *Leuconostoc citreum* bacteria was observed after 120 s, but the acidity caused by NO_x formation must be lowered under a critical value of pH 4.7. However, if they added bacteria to the water exposed to plasma 10 min earlier, no inactivation was observed despite this water contained sufficient concentrations of NO_x and H_2O_2. In the next work of Oehmigen et al. (2010), the properties of water which was exposed to a surface dielectric barrier discharge in air at 10 kV and 20 kHz, especially its disinfectant ability, were thoroughly investigated. The authors determined the kinetics of NO_x formation, causing subsequent formation of nitrous HNO_2 and nitric acid HNO_3 formation, strong acids responsible for acidification: in physiological saline, pH decreased to values between 2 and 3 for 30 min, whereas in phosphate buffered saline (PBS), no acidification was observed. Simultaneously, H_2O_2 was formed reaching concentrations of 3 mg l^{-1} to 18 mg l^{-1}. *S. aureus* and *B. atrophaeus* spores were also incubated in hydrochloric acid and nitric acid solutions to verify the bactericidal effect of acidity alone, but no inhibition of these bacteria was observed. Only *E. coli* was inactivated after 30–60 min of incubation, in concentrated HCl and HNO_3 solutions at pH 2. The authors conclude that an acidic environment, even after addition of nitrate ions, is not capable of causing the inactivation of microorganisms comparable with plasma treatment. In a closely related paper of Oehmigen et al. (2011), the formation of peroxynitrous acid ONOOH as the possible stable disinfection agent was suggested for the first time.

Traylor et al. (2011) monitored the microbicidal action of water exposed to DBD for several days. The correlation between the H_2O_2 and nitrite levels and inactivation of *E. coli* for 15 min exposition to the exposed water was found, but not for 3 h exposures, which yielded higher and sustained microbicidal effect persisting over 7 days. Julák et al. (2012) observed the rapid acidification of pure water up to pH 2, the kinetics of other products formation was also determined. The microbicidal effect decreased only weekly after 4 weeks of storage, although O_3 completely and H_2O_2 almost disappeared. Exposed and stored liquids inactivated *S. epidermidis* and *E. coli* within 10 min of incubation, whereas yeast *C. albicans* needs at least 1 h. The artificial mixtures of reactive compounds displayed a similar effect but somewhat lower effect as exposed water, so that acidity, hydrogen peroxide and ozone may be considered mainly responsible for the microbicidal action, but the presence of still unidentified additional compound(s) remains possible.

Peroxynitride ($ONOO^-$) was suggested as the one of possible remaining agents in post-discharge processes. It vas reported by several authors, namely Brisset and Hnatiuc (2012), Nätali et al. (2012), and Machala et al. (2013). Lukes et al. (2014) detected it by aqueous-phase chemistry using phenol as a chemical probe. Nevertheless, there is the problem of limited stability of peroxynitrous acid in acid solutions.

3. What is it good for and possible applications

3.1. Waste water cleaning

The NTP generation mechanisms in liquids are a little bit different from those in air and beyond the active particles, electrical field and radiation: the microbicidal effect is also moderated by acoustic and shock waves. There are two works describing the opportunities of NTP in waste water treating. Rowan et al. (2007) developed a system based on pulsed plasma gas discharge, used for the novel decontamination of chilled poultry wash water. Treatment of this water for 30 s reduced the populations of *E. coli*, but also of human pathogens *Salmonella enterica*, *Listeria monocytogenes* or *Campylobacter jejuni* and *Campylobacter coli* to levels (≤8 log CFU/ml), which were not detectable. This treatment also provided a significant reduction (≥3 log CFU/ml) of *Bacillus cereus* endospores. The work of Kim et al. (2003) reflects the food industry's interest in ozone usage, recently accompanied by the US government approving ozone as a safe antimicrobial agent on food including meat and poultry. The chemical and biological oxygen demands of processing water were decreased by using ozone as a decontamination agent. This also improves the reusability of waste water and allows implementation of environment-friendly operations.

3.2. Ready-to-eat food treatment and food packaging

Ready-to-eat foods are those you don't need to cook. Although this kind of alimentation is convenient, it requires special handling to ensure its safety.

By definition, ready-to-eat foods are commercial food products intended for easy consumption. Products intended as convenient for ready-to-eat foods may be prepared for distribution: a) as hot, ready-to-eat dishes; b) at room-temperature, shelf-stable products; c) and refrigerated or frozen products requiring minimal preparation, most often just heating. These products ought to be handled with special care, the rules of safety in food preparation and sanitation should be strongly followed.

Food spoilage microorganisms and especially food-borne pathogens represent a main problem in food industry as an important public health threat and economic impact. There are many sterilization methods to eliminate these microorganisms, based mainly on heating. Unfortunately, they sometimes cause side-effects by affecting adversely nutritional values, sensoric properties and even function of treated foods. NTP may be a new discipline in food processing.

Describing various types of ready-to-eat foods is almost impossible. They include not only a variety of soft cheeses, but also plenty of vegetable, fruit or fish salads of various types, smell and tastes, many pre-cooked and/or meat or seafood, just to mention the most consumed ones. One of the first applications of atmospheric plasma on contaminated apples, cantaloupe and lettuce was published by Critzer et al. (2007). The food matrices were inoculated by a mixture of *E. coli* O157:H7, *L. monocytogenes* and *Salmonella* (7 log CFU per sample). *E. coli* O157:H7 populations were reduced after 30 s and 1 min exposures by >1 log and after >2 min exposure >2 log. *Salmonella* populations were reduced after 1 min by >2 log. The longer exposures (3 and 5 min) yielded >3 log and >5 log reductions. Perni et al. (2008) examined the decontamination effect of NTP on pericarp of melon and mangoes inoculated by *S. cerevisiae*, *P. agglomerans*, *Gluconobacter liquefaciens*, and *E. coli*. It was observed that *S. cerevisiae* was the most resistant. *P. agglomerans* and *G. liquefaciens* disappeared below the

limit of detection (3 log) after only 2.5 s of exposition on both fruits, whereas to reach the same level of inactivation of *E. coli* required 5 s. Song et al. (2009) investigated the influence of food matrix. They inoculated a mixture of three *L. monocytogenes* strains into sliced cheese and ham and exposed them to plasma for 60, 90 and 120 s. Microbial log reduction appeared to be directly proportional to input power and exposure time. The results confirmed that inactivation of *L. monocytogenes* depends strongly on the type and structure of investigated of food. The limitations of the NTP process for food sterilization are that in treatment of bulky and irregularly shaped food, restricted volume or and size of the investigated material should be considered. Microbial inactivation occurs usually on the treated surface, because penetration of plasmatic reactive particles into the deeper layers of food is limited. The seeds of *Brassica napus* were contaminated by endospores of *B. atrophaeus*, 10^8 CFU/ml and afterwards treated with DBD plasma (Schnabel et al., 2012). Besides the seeds, three types of non-biological materials (molecular sieve, glass beads, and glass helices) were tested. After a 15 min operation reduction rates between 0.5 and 5.2 log were achieved. The viability of the seeds was not reduced. Bermúdez-Aguirre et al. (2013) exposed lettuce, carrots and tomatoes contaminated by a pathogenic strain of *E. coli* to NTP and assessed the microbiological quality after processing, using Hunter's color parameters. The degree of inactivation was dependent on the intensity of inoculation, i.e., it was easy to inactivate low bacterial counts. The color of the treated product was not affected. The structure of exposed microbial cells displayed extensive electroporation, cell membranes were deformed, disrupted and partially lost. Niemira and Sites (2008) contaminated the surface of Golden Delicious apples with pathogenic strains of *E. coli* O157:H7 and *Salmonella* serovar Stanley and exposed them to NTP generated in a gliding arc. Reductions after 3 min ranged from approximately 3 log CFU, close to the detection limit. Ragni et al. (2010) reported the method of decontamination of egg shells from *Salmonella enteritidis* and *L. monocytogenes*. Baier et al. (2013) investigated the NTP on the leaves of corn salad (*Valerianella olitoria*) that were inoculated by 50 μL of *E. coli* K12 suspension. Two concentrations of cells were applied: 10^7 CFU/cm^{-2} and 10^4 CFU/cm^{-2}. The NTP effect was tested with several generator power (from 10 to 40 W). At a moderate generator power of 20 W, bacteria with lower initial load could be inactivated by 3.6 ($\pm$0.6) log/cycles within 15 s of treatment; whereas at a higher initial load of 10^7 CFU/cm^{-2}, bacteria were reduced by 2.1 ($\pm$0.2) log/cycles after 30 s.

Fernández et al. (2013) studied the influence of growth phase, temperature of incubation and treatment with chemicals on the inactivation of *S. enterica* serovar Typhimurium treated by NTP. A 2 min treatment under optimal conditions, resulted in a 2.7 log-reduction of *Salmonella* viability. The growth phase, temperature of incubation and chemicals did not influence the inactivation. Selcuk et al. (2008) used low-pressure NTP to inactivate and/or eliminate species of *Aspergillus* and *Penicillum* artificially inoculated onto the surface of seeds. The plasma treatment reduced the fungal attachment to seeds within 20 min of exposure by 3 log below 1 % of the initial concentration, the germination quality of the seeds was not affected.

Leipold et al. (2010) described the use of plasmas at atmospheric pressure for the decontamination of a grinding machine in the meat industry. A rotating knife was inoculated with *Listeria innocua* and exposed to plasma produced by DBD in ambient atmosphere. The exposure was performed on the rotating cutting knife, so that the exposure of its whole surface was ensured. A log 5 reduction of *L. innocua* is obtained after 340 s of plasma operation. This arrangement makes it possible to decontaminate the tool during grinding operation. After 340 s of exposure, a log 5 reduction of testing bacteria count was achieved.

Recently Afshari and Hosseini (2014) in their review appraised the applications of nonthermal plasma as a new food preservation method with a great potential in the future.

Decontamination of fresh food packed in a sealed package is one of NTP special applications. Using the DBD with properly ordered electrodes, the NTP may be inductively generated directly inside the container. The DBD ozone generation system (PK-1) was used by Klockow and Keener (2009) to decontaminate fresh spinach inoculated with *E. coli* inside a sealed package. After 5 min of exposition the reductions of 3–5 log 10 CFU/leaf was observed after 24 h of storage. However, in this setting, the color quality of spinach has decreased too much. Ziuzina et al. (2013) treated *E. coli* suspension placed in wells of a microtiter plate and enclosed in a sealed package by the dielectric barrier discharge. The effects of 20 s of direct and 45 s of indirect plasma treatment resulted in a complete bacterial inactivation of 7 log CFU/ml was achieved after 45 s of indirect and 20 s of direct plasma action.

The effect of microwave processed plasma air (PPA) on seven different microorganisms spiked on apple (peal and pulp), strawberry, lamb's lettuce and carrot was studied by Schnabel et al. (in press). They presented very promising results, because after only 7 s of direct plasma activity followed by 15 min incubation in PPA the microbial load was reduced more than 6 log. The sensory properties, texture and appearance of tested fruits and vegetable remained unaffected. In the same year Baier et al. (2014) published a substantial study about cold plasma impact on several factors: chlorophyll fluorescence imaging, postharvest quality and antibacterial effect of NTP. They employed argon plasma-jet, that proved to be a suitable antimicrobial agent with a high potency to reduce the microbial load of bacterial pathogens on fresh produce. Surowsky et al. (2014) confirmed the cold plasma effect on *Citrobacter freundii* added to apple juice. The initial bacterial concentration was reduced by about 5 log cycles after a plasma exposure of 480 s using argon and 0.1% oxygen plus a subsequent storage time of 24 h. In a recent work of Misra et al. (2014), the strawberries were treated by the DBD produced directly in ambient air at 42% relative humidity, inside a closed and sealed package. The background microflora of strawberries consisted of mesophilic aerobic bacteria and fungi (molds, yeasts) which were reduced within 5 min by 2 log 10, the color and firmness of strawberries were not significantly affected. These results together with many other data concerning NTP effect on solid and liquid food systems are summarized in Surowsky et al. (2014b). Authors gathered reliable bases about the advantages of NTP treatment and their future perspective usage in the food industry.

3.3. Treatment of packaging materials

The low temperature of NTP makes it the method of choice particularly suitable for various thermolabile substance treatments. In biotechnology, this holds especially for the treatment of plastic foils, films or fabrics where NTP implicates both decontamination and surface modification, namely the increase of surface energy resulting consequently in lower hydrophobicity and increased wettability.

In Novák et al. (2007) and Ataeefard et al. (2009) the surface of low-density polyethylene (PE) was modified by DBD and RF discharge in Ar, O_2 and N_2 atmosphere. The results showed that in all cases the surface wettability was improved. In Akishev et al. (2008a) the surface of polypropylene (PP) was modified using the plasma jet in air and N_2 with similar results of wettability improvement. Moreover, a theoretical model for plasma processing of PP foil was described here. Píchal and Klenko (2009) presented similar results with polyester textile fabrics treated in open air DBD. In all the cases the modification effect is not permanent, but the material returns by aging to original state. During the first days after treatment a fast recovery occurs, but its progress decelerates later and an almost original state before treatment is reached eventually.

Schneider et al. (2005) used various NTP sources for the decontamination of PET foils contaminated by *B. subtilis* spores and confirmed the decrease of 5 orders of magnitude in several seconds. However, for practical application, the atmospheric pressure devices presented next are more suitable. Muranyi et al. (2007) followed the microbial inactivation efficiency of DBD against Gram-positive *S. aureus*, Gram-negative *E. coli*, *Salmonella* and against spores of *B. atrophaeus*, *Clostridium botulinum*

and the fungus *A. niger* on polyethylene terephthalate (PET) foils. A high reduction of microbe counts was observed for the vegetative cells, reaching at least 6.6 log 10 within 1 s. *A. niger* appeared to be the most resistant tested species with an inactivation rate of about 5 log 10 in 5 s. In the following study Muranyi et al. (2008) investigated the influence of humidity on the inactivation efficacy of a DBD in air against *A. niger* and spores of *B. subtilis*, again spread on PET foils. For *A. niger*, the spores were mostly inactivated at a high relative humidity of 70% (approx. 2 log 10). On the contrary, slightly poorer inactivation of *B. subtilis* was observed at high gas humidity. The work of Muranyi et al. (2010) generalized these results: using different microorganisms and different polymer films, the suitability of the method for polymer film treatment was demonstrated. Yang et al. (2009) used oxygen NTP to inactivate *P. aeruginosa*. The contaminated PET sheets (size 25 mm × 50 mm) were placed in a plasma reaction tube, and treated in three areas: the discharge area (samples distanced 15 cm from the center of an induction coil), afterglow area (samples distanced 55 cm) and remote area (samples distanced 75 cm). The results showed that after a treatment of 30 s the numbers of CFU decreased by 4.2, 3.8 and 2.6 orders of magnitude. In the recent work of Stepczyńska (2014), the corona discharges were used for the decontamination of several microorganism species deposited onto a polylactide (PLA) packaging film. A reduction of over 2 orders of magnitude occurred for *S. enteritidis*, *P. aeruginosa*, and *Penicillium chrysogenum* only. On the other hand, perceptible biocidal effect was not observed for *E. coli*, *B. subtilis* and *S. aureus*.

A study of other polymer materials is presented in Yun et al. (2010). This study was focused on *L. monocytogenes* inoculated onto disposable food containers including paper cups, aluminum foil and disposable plastic trays. On plastic trays, there were no viable cells detected after 90 s of treatment. However, in aluminum foil and paper cups, only three decimal reductions of viable cells were achieved. Hence, to achieve satisfactory inactivation, it is crucial to determine the optimal conditions for treatment of a particular wrapping material type.

Radetić et al. (2008) studied the possibility of using an open air corona discharge to activate the surface of fabrics made from the polyester (PES) and polyamide (PA) fibers. Onto these fabrics, silver nanoparticles from colloids were loaded in order to improve their antibacterial properties.

The deposition of silver nanoparticles on treated fabrics was facilitated, which was exhibited by better antibacterial properties as compared with the untreated fabrics. In order to improve the laundering durability to an acceptable level, the use of strongly concentrated silver colloids is needed.

3.4. Medicine

The possible applications of NTP in medicine for microbial decontamination, chronic wound healing and tissue regeneration, blood coagulation and cancer treatment were reviewed in an extensive article of Fridman et al. (2008). It is focused on nonthermal plasma treatment of various diseases, describing the successful experiments carried out on animals and humans, on dead and living tissues. The recent review of Yousfi et al. (2014) summarized the most commonly studied areas of NTP. Here, some selected representative papers are presented.

3.4.1. Chronic wounds and skin infections

The NTP can serve as an antifungal treatment. The shortening of skin lesion persistence along with suppression of subjective discomfort and etiological agent was observed. The possibility of open and chronic wound healing represents and constitutes a challenge not only from a therapeutic, but also from an economical point of view. The action of NTP seems to constitute effective and innovative access. The periodic therapy by nitrogen oxide (NO) generated in air plasma reduced the final healing time of venous trophic ulcers by 2–4 times (Stoffels, 2006). In the case of a diabetic foot ulcer, plasma therapy reduced the necessity of amputation by 2 times (Shulutko et al., 2004). Another interesting paper of Heinlin et al. (2010) showed the results obtained from a 61-year-old patient with venous ulcers: the short periodic treatment by microwave NTP for 2 min daily resulted in a spectacular and significant ulcer reduction after the 23rd day.

Plasma can also be useful in treatment of some skin disorders, such as dermatomycoses or dermatitis with acneiform eruption. Švarcová et al. (2014) reported a medical case of dermatomycosis caused by a zoophilic strain of *T. interdigitale* treated by NTP by DC driven cometary discharge, where the shortening of skin lesion persistence along with suppression of subjective discomfort and etiological agent was observed. Daeschlein et al. (2012b), or Julák and Scholtz (2013) have reported the possibility of NTP to disinfect the skin in several minutes.

Experiments showed that NTP enables efficient and contact-free but painless disinfection, acting also in microscopic pores and causing no damage or deterioration of healthy tissues. The interaction of NTP and living tissues, its interaction with living cells and its catalytic participation in the cell repair process seems to be proved, the mechanism(s) of these interactions remains poorly identified and analyzed.

3.4.2. Blood coagulation

Cauterization as common processes used to accelerate blood coagulation, also usually damages the surrounding tissue due to high temperature. Studies reported by Kalghatgi et al. (2007) or Fridman et al. (2008) have shown that blood coagulation can be also accelerated by NTP treatment, which triggers platelet activation both in vitro and in vivo.

3.4.3. Cancer treatment

Several pilot works by Nuccitelli et al. (2006), Fridman et al. (2007), Kim et al. (2009) and Zhang et al. (2008) demonstrated that NTP can induce selective apoptosis and/or necrosis in cells of melanoma and liver cancer at least in artificial cultures in vitro. Fridman et al. (2008) proved a similar effect on human melanoma skin cancer cells, inactivated by DBD plasma produced in ambient atmosphere. The direct action of low plasma doses on the cells was considered by these authors as a sufficient promoter of apoptosis rather than a source of poisoning of the solution surrounding the cells. These works, devoted to in vitro experiments, were followed by in vivo studies. Preliminary results published by Vandamme et al. (2010), present the consequences of in vivo exposure of malignant cells to NTP generated by pulsed DBD in air at ambient conditions. The experiment was arranged as follows: specific female mice were under well controlled conditions given malignant cells subcutaneously. After growing a tumor to a certain volume, mice were exposed daily with pulsed plasma. After five days of exposure, a significant lowering of tumor volumes was observed.

These preliminary and sparse results appearing in literature predicate the feasibility of low-temperature plasma to inactivate some malignant cells both after in vivo and in vitro exposures and are summarized in a recent review paper by Schlegel et al. (2013). The results suggest the promising direct effect of low-temperature plasma as a potential pharmaceutical tool against cancer, but the mechanisms involved in its action are far from being understood and further extensive research in needed in this field.

3.4.4. Dentistry

Among numerous applications in dentistry, Sladek et al. (2004) suggested the use of the plasma needle for cleaning and disinfection of dental cavity tissue or tooth root canal. This proposal was verified by Sladek et al. (2007), who demonstrated the effective inactivation of biofilms formed by the key cariogenic bacterium *Streptococcus mutans* by the plasma needle. The usefulness of NTP in dentistry was further suggested by Kovalóvá et al. (2014). Using direct current corona discharges, they demonstrated the reduction of dental streptococci biofilm up to 3 logs within 10 min of exposure time. Electrostatic

spraying of water through the discharge hastens this effect. These procedures do not influence or alter the tooth surface material composition or structure significantly. An interesting application of NTP to tooth bleaching was described by Lee et al. (2010).

Recently, a special issue of Clinical Plasma Medicine appeared, containing an extensive review of plasma application in dentistry (Seunghee and Young-Seok, 2014).

3.5. NTP side effects

Surowsky et al. (2014b) accumulated evidence concerning plasma-related impact on food components and properties. Data from 23 publications recording changes of food and enzyme properties indicated only insignificant alterations of individually measured properties such as pH, color and cell structure. In medicine, Heinlin et al. (2010) reported, that no side effects have been observed at any time in patients with chronic and infected wounds, which were treated daily by argon plasma exposure. Also Fridman et al. (2008) and Daeschlein et al. (2012a) observed no damage of skin barrier during a series of plasma treatments, and that plasma treatments are generally well-tolerated. However, as the general rule for both food and biomedical application, careful and extensive tests are recommended for each specific case.

5. Conclusions

Based on all the previous information, NTP appears to be a powerful and useful tool for decontamination and disinfection. The presented properties of NTP are well documented in many papers and there is no doubt that NTP has high potential to be applied in biotechnology. However, it is evident, that a lack of standard test procedures and comparable data calls for unified testing procedures, selection of suitable test microorganisms, and mainly for more comprehensive standardized research. The types of the decontamination technologies used for special purposes are as diverse as the range of plasma sources used and the plasma use parameters. All of these conditions influence and vary the composition of plasmatic particles and the emitted radiation acting as microbicidal agents. Together the different test microorganisms, variable microbiological test methods and procedures result in an inhomogeneous picture of the state-of-the-art techniques in this field.

A noticeably better situation is found in the field of plasma medicine, which is not strictly the area of biotechnology, but was also briefly described in this review to provide a more complete picture of NTP bio-applications. In medicine, unlike in biotechnology, there are some completed testing procedures documenting the healing abilities of NTP. There are a few NTP sources certified to be used in medicine. This moves NTP closer to common medical use than its utilization in food technology.

In conclusion, the authors would like to take into account the growing popularity of raw food that is prepared without any thermal processing. Besides the food industry, where food treatment is done in large scales, compact easy-to-handle NTP plasma sources may be used at home to prepare germ-free food for daily consumption both for adults and children. Nevertheless, the design of such devices is by no means only from the realms of science fiction. However, for a successful deployment of NTP technology, a lot of hard work will be required by multidisciplinary teams consisting of both scientists and engineers in order to bring a useful gadget to market within a price range comparable to currently available microwave ovens.

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