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Review Article

Antimicrobial Photodynamic Therapy: Novel Concept for Foodborne Pathogens

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ABSTRACT

Changes in agricultural practices, individual diversity, the considerable size of the global food trade, immigrant and tourist circulation, with microorganism transformations have led to the formation of microorganisms that are resistant to chemicals and implementations used, especially antibiotics. Antimicrobial photodynamic therapy (aPDT) is an approach based on the interaction of a natural/synthetic photosensitizer, a suitable light source, and molecular oxygen, and the cytotoxic effect of reactive oxygen species resulting from this interaction on the target microorganism. The benefits of this method, which has found its place in medical terms by treating oral biofilms, superficial lesions, and chronic sinusitis, are limited by problems of low cell/tissue penetration, poor selectivity, non-thermal effect, and off-target damage. Despite similar practical problems in food science, developing technology is expected to encourage new studies on pathogen inactivation in food matrices, reducing the microbial load to safe levels, extending shelf life, and preventing quality loss.

Keywords: *Antimicrobial photodynamic therapy, Photosensitizers, Free radicals, Foodborne pathogens*

Antimikrobiyal Fotodinamik Terapi: Gıda Kaynaklı Patojenler için Yeni Konsept

ÖZ

Tarımsal uygulamalardaki değişiklikler, bireysel farklılıklar, küresel gıda ticaretinin hatırı sayılır büyüklüğü, göçmen ve turist dolaşımı, mikroorganizma transformasyonları ile başta antibiyotikler olmak üzere kimyasallara ve kullanılan uygulamalara karşı dirençli mikroorganizmaların oluşmasına yol açmıştır. Antimikrobiyal fotodinamik tedavi (aPDT), doğal/sentetik bir ışığa duyarlılaştırıcı, uygun bir ışık kaynağı ve moleküler oksijenin etkileşimi ile bu etkileşim sonucu ortaya çıkan reaktif oksijen türlerinin hedef mikroorganizma üzerinde sitotoksik etkisine dayanan bir yaklaşımdır. Oral biyofilmleri, yüzeysel lezyonları ve kronik sinüziti tedavi ederek tıbbi anlamda kendine yer bulan bu yöntemin faydaları, düşük hücre/doku penetrasyonu, zayıf seçicilik, termal olmayan etki ve hedef dışı hasar sorunları nedeniyle sınırlıdır. Gıda bilimindeki benzer uygulamaya yönelik sorunlara rağmen gelişen teknolojinin, gıda matrislerinde patojen inaktivasyonu, mikrobiyal yükün güvenli seviyelere indirilmesi, raf ömrünün uzatılması ve kalite kaybının önlenmesi konularında yeni çalışmaları teşvik etmesi beklenmektedir.

Anahtar kelimeler: *Antimikrobiyal fotodinamik tedavi, Işığa duyarlılaştırıcılar, Serbest radikaller, Gıda patojenleri*

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I. INTRODUCTION

Latterly, bacterial infections are an increasing problem globally recognized as a burden on public health. Such infections constitute high mortality for patients with traumatic lesions or who had surgery and farm animals. Mutations that allow microorganisms to multiply exponentially and survive in the presence of any antimicrobial drug increase their regeneration capabilities and enable them to become dominant in the population quickly. In this respect, inappropriate prescription or uncontrolled usage of antibiotics exacerbates the threat of microbial resistance. Also, biofilm formation stands out as a factor contributing to the rise in microbial resistance. The blooming of biofilms in clinical settings, buildings, monuments, facilities, and technical complexes poses serious sanitary consequences as well as aesthetic, ecological, and economic loss.

Microorganisms such as bacteria and filamentous fungi, which have spore forms and are more resistant to inactivation than planktonic microorganisms, can similarly be considered a threat to human health. For this reason, significant amounts of biocides and their derivatives are used to combat the growth of planktonic and biofilm-embedded microorganisms in physiological fluids or solid surfaces [1]. Nevertheless, the chronic toxicity of the chemicals mentioned and the environment, animal, and human stress that contradicts the one health approach indicates that they are far from a sustainable formula for the solution to the problem. The adaptation abilities of microorganisms caused by their reproduction rate are the main factors in developing their resistance to biocides.

There is a consensus across the scientific community that new strategies must be developed to combat these microbial entities. From this point of view, 'Antimicrobial Photodynamic Therapy' (aPDT) has been progressing. Bacterial inhibition of photodynamic therapy, initially considered only as an anticancer technology, has revealed aPDT as a new field. This method relies on the cell-toxic effect of reactive oxygen species (ROS) produced due to the stress caused by a light source, photoactive chemicals, and molecular oxygen on the cell. Recently, in response to the requirements and expectations of the modern age, it has emerged as a noninvasive treatment alternative and has gone beyond its medical axis and has the opportunity to be tested in sectors such as food and agriculture.

The purpose of this review is to systematize current studies on the role of photodynamic therapy, especially in the elimination of pathogens that threaten food safety, within the general framework of the application.

II. PHOTODYNAMIC THERAPY

Photodynamic therapy as a cure method in medicine and surgery dates back to ancient times in Egypt, Greece, and India. Ancient civilizations used sunlight to empirically treat various skin problems, using light interaction with biological tissues. However, over time, such attempts have become increasingly rare over the centuries and were somewhat explored again by Western civilization in the early 1900s. The emergence of modern photodynamic or photoactivated therapy stands on the mutual effect of a photosensitive agent with a light resource by using a non-toxic dye and low-intensity visible light. With the presence of oxygen, this combination produces some cytotoxic molecules. Irradiation with a particular wavelength of light cause the production of singlet oxygen that disrupts the microbial cell wall and further inactivation [2].

Oscar Raab and his PhD advisor H. von Tappeiner introduced the idea of cell death brought on by the interaction of chemicals called photosensitizers with light. Raab unexpectedly discovered that combining acridine red and light had a phototoxic impact on *Paramecium infusoria* while researching the effects of acridine dye on paramecium cultures. The outputs of the experiments using low concentrations of acridine red could not be replicated due to inconsistency despite many repetitions. However, Raab and Tappeiner found that the observed toxicity was linked with the time of day and the sum of sunlight, which were the only changed parameters. Thus, Raab demonstrated the potential of

photosensitive compounds to be used as toxicants for biological systems in light availability. The fact that dye had a stronger toxical influence on paramecium samples on sunny days instead of cloudy days led him to note that a photosensitizer is responsible for the photodynamic action in the presence of energy from the bright sun [3].

A. MECHANISM OF ACTION

Light, a non-toxic photosensitizer (PS) and molecular oxygen are essential system components for the design of antimicrobial photodynamic therapy [4]. The basic principle includes the penetration of photosensitizing dyes into the relevant infected/contaminated tissue, followed by the generation of cytotoxic ROS due to exposition to visible light. ROS can irreparably harm cellular integrity by oxidizing microorganisms' structural proteins, lipids, enzymes, and nucleic acids [3]. After irradiation and photon absorption, the photosensitizer can transform from the low-energy and stable configuration initial (ground) state (PS*) to the short-lived, more reactive, excited single-state (1PS*) or it may return to its initial level with a loss of energy by fluorescence or emitting heat. As a third response, it can transition to a higher energy triple state (3PS*). In this case, two distinct chemical reaction pathways-Type I electron transfer and Type II energy transfer-that can take place simultaneously may be encountered. In a type I reaction, 3PS* absorbs an electron (e^-) from a nearby reducing molecule (R); this triggers an electron transfer that results in the superoxide anion radical ($O_2^{\bullet}$), and subsequent reduction results in the formation of additional cytotoxic ROS that include hydrogen peroxide (H_2O_2) and hydroxyl radical ($HO^{\bullet}$). Direct energy transfer from 3PS* to molecular oxygen's starting state ($3O_2$), which is then changed into singlet oxygen, occurs in a type II reaction ($1O_2$) [5]. The ROS produced includes $O_2^{\bullet-}$, H_2O_2, $HO^{\bullet}$ and $1O_2$. $HO^{\bullet}$, and $1O_2$ are the most reactive and cytotoxic, but at the same time have the shortest diffusion distances. PS can produce a substantial amount of $1O_2$ molecules, especially according to the $1O_2$ quantum efficiency, the characteristics of the surroundings, and the realization of Type I and Type II mechanisms.

Aiming at the destruction of vital components or structures in microorganisms is a principle to direct the efficacy of aPDT. DNA degradation induced by PS and light in target microorganisms causes the over-stranded fraction of the plasmid to break into single- or double-stranded DNA. Membrane damage with subsequent loss of selective permeability, denaturation of cytoplasmic proteins, impaired cell wall synthesis or potassium (K^+) decrement is other proposed reasons for cell demolition [6].

B. FACTORS OF PHOTODYNAMIC THERAPY

B. 1. Light Properties and Sources

The cellular structures of biological tissues vary and contain many substances and organelles explaining their inhomogeneity. Highly pigmented tissues, for instance, might limit the depth at which light can enter the tissue. An infected tissue's turbid media and light scattering lead to a light beam directionality and propagation being off-course [3]. The depth at which light reaches the microorganism in tissue depends on the optical features of the tissue and the wavelength of the light. Cell chromophores or extracellular substances can reflect or absorb certain photons that penetrate tissues [7]. Because of the size of the particles that most thoroughly permeate the tissues, red and near-infrared lights accomplish light absorption better. The efficacy of PDT correlated to the exposure duration, light wavelength, and sort of tissue.

Considering the variability of the preferred light sources in PDT, the correct selection of this parameter is one of the cornerstones of the photoinactivation mechanism: Conventional lamps (metal-halide, xenon, tungsten halogen, etc.), light-emitting diodes (LEDs), and lasers [8]. Specially lasers are quite effective and commonly used in medical practice. On the other hand, their high expense puts them a not feasible alternative, especially for real-time food industry applications. Compared to lasers, LEDs offer a slightly broader emission spectrum and price less. In this respect, LEDs have become more appealing to the field of food technology (primarily for post-harvest storage, food safety, and food production) with their high cost-benefit ratio, low maintenance, endurance, and reduced negative perception on the strength of thermal effects.

Conversely, LEDs, lasers, and halogen lamps benefit from being spectrally filtered to match any PS. Despite that, they cannot be coupled to optical fiber bundles or liquid light guides efficiently, and they produce more heat. Every therapeutic use of PDT in the patient's body should consider the heating impact from a certain light source. The administered energy dose will raise the temperature, which might lead to tissue injury, depending on the length of the exposure and the type of light source employed. In brief, for the irradiation of a particular PS, intensity, light distribution, and the spectral emission mode of the relevant light source (directly or indirectly like fiber optic cable) are of greater importance than the light source itself.

B. 2. Photosensitizers

Photosensitizers (PS) are dyes that can receive energy from a light source and transport this energy to different targets [9]. For a sufficient PDT application, the choice of the PS factor has of great importance. There are several criteria to be considered for this purpose, including appropriate photosensitizing properties, high water solubility, low dark toxicity, high photo and storage stability, low long-term sensitivity, high target selectivity, and low production cost.

Varied kinds of PSs, such as phenothiazine dyes (methylene blue, toluidine blue O), phthalocyanine, porphyrin, bacteriochlorins, xanthene and, curcumin have been demonstrated to have significant inactivation effects. Due to their similar chemical and physicochemical properties, the most widely employed dyes for PDT are methylene blue and toluidine blue [10]. Toluidine blue O is a blue-violet solution that stains connective tissue glycosaminoglycans and proteoglycan granules in mast cells. Methylene blue is blue in an oxidizing environment and is a redox indicator that becomes colorless when reduced. Light-coupled methylene blue has also been reported to be useful in inactivating seasonal influenza, *Helicobacter pylori*, and *Candida albicans* [11]. Very efficient photosensitizers for inactivating Gram (+) and Gram (-) periodontopathic bacteria that led to periodontitis include both methylene blue and toluidine blue O [12]. Investigations and syntheses of methylene blue analogs and other kinds of photosensitizers have been/are being done to get beyond the practical limitations brought on by these phenothiazine dyes' toxicity to non-target cells such as red blood cells [3][11].

Organic PSs used in PDT were selected from the phenothiazinium group containing methylene blue and toluidine blue O. Through the absorption spectrum in the red region of the light, these new PSs and their structural derivatives show their efficacy in tissues and have less toxicity than other PSs. Another group includes macrocyclic molecules, often positively charged, hydrophilic, and have strong singlet oxygen quantum yields. Many studies have been conducted on changes to their chemical composition, particularly for porphyrins and phthalocyanines. PSs having a structure resembling fluorescence, such as rose bengal, erythrosine, and eosin Y, are collected by halogenated xanthenes. These anionic chemicals can confine their contact with bacterial cells and their photodynamic effects while having strong singlet oxygen quantum yields. Benzofurans, coumarins, anthraquinones, furanocoumarins, and flavin derivatives are naturally occurring compounds. Curcumin, riboflavin, and hypericin are characterized by an absorption spectrum in white light or UV-A.

Dias *et al.* [3] concluded that as an actively working PS, curcumin relies on the concentrations used, the types and fluxes of light sources, the co-solvent, the target microorganism species, and the growth pattern of homogeneous microorganisms. The authors noted that while it may be difficult to make sense of the varying parameters and detailed protocols, they expect using curcumin and its analogs to improve existing photodynamic protocols for infectious diseases, surface sterilization, and holistic food safety. Curcumin's effectiveness in photoinactivation of methicillin-resistant *Staphylococcus aureus* (MRSA) and *Staphylococcus aureus* (MSSA) was investigated by Ribeiro *et al.* [13] observed that MSSA was completely photoactivated at curcumin concentrations between 5.0 and 20.0 M after 20 minutes of incubation and under various blue-light power densities. They deduced that the integration of curcumin with LED light in hospital settings might be a technique for eliminating pathogens like MRSA. Based on the quantity of photons absorbed, Le *et al*. [14], investigated the antibacterial activity of curcumin with aloe-emodin under PDT with the demonstration of decreased *S. aureus* and *E. coli* counts by around 2.3 and 1.1 log units, respectively.

Dhanalekshmi *et al*. [15] in their comprehensive evaluation of non-toxic, high photostability, inorganic noble metal nanoparticles (NPs), emphasize that noble metals such as silver and gold are remarkable due to their unique optoelectronic properties depending on their size and shape. They pointed out that in addition to coating inorganic/organic materials on the noble metal, making the NPs less harmful in terms of toxicity and biocompatibility, coating inorganic/organic complex NPs shields the noble metals, stabilizing them against chemical corrosion and promoting ROS generation. Ren *et al*. [16] loaded brusatol (Bru) on the surface of UVA-sensitive zinc oxide (ZnO) coated magnetic nanoparticles (Fe_3O_4ZnO-Bru) and as a result of the study, Fe_3O_4ZnO-Bru was successfully synthesized and photodynamic therapy was combined with photochemotherapy, which showed a higher inhibitory effect on carcinoma cells. Another nanoparticle-based study dedicated to the rise of nanotechnology, to get beyond the drawbacks of using porphyrin as PS and to determine the effectiveness of PDT, Tsolekile *et al.* [17] conjugated ZnCuInS/ZnS quantum dots (QDs) to 5,10,15,20-tetrakis(3-hydroxyphenyl) porphyrin (mTHPP). QDs, mTHPP, and conjugate activity against the murine metastatic melanoma cell line were assessed in the presence and absence of LED irradiation. In comparison to bare QDs (19%) and mTHPP (1%), the conjugate showed the highest reduction in cell viability after LED exposure (72%).

B. 3. Molecular Oxygen

The desired functioning of the photodynamic therapy mechanism is related to the presence of emerging ROS [6]. In this respect, singlet oxygen ($1O_2$) converted from molecular oxygen by PSs is responsible for detrimental cellular effects. Singlet oxygen destroys cell organelles and results in the programmed death of cells (apoptosis). Aerobic bacteria employ molecular oxygen (O_2), a nonpolar, tiny molecule that diffuses through the cellular membrane, for oxidation and respiration processes. Oxygen enters the reduction process for energy production after passing through the membranes, causing oxidative phosphorylation and ATP synthesis, and performing the initial step of the ROS formation cycle.

B. 4. Others

Molecular oxygen, PS, and light are essential conditions for PDT implementation. The combination of these three elements, each of which is essential, determines how effective PDT will work. Photosensitizer is the most significant component in the mechanism of PDT owing to its operation and safety issues, but oxygen is frequently the most challenging to manage. However, from the perspective of food substrates, the types of food components, environmental restrictions, or process limitations will also have an influence, thus, acidity, temperature, and buffer agents must be taken into consideration to ascertain whether PDT can be applied in real-life utilization.

III. MEDICAL AND DENTAL IMPLEMENTATIONS OF PDT

A. DENTAL APPLICATIONS

Plaque biofilm, or bacterial biofilms on the tooth surface, is a major contributor to the development of periodontal disease, endodontic infections such as peri-implantitis, caries, and several other problems beyond the mouth cavity. Dental plaque that has formed on the surface of teeth from Streptococcus mutans in the oral cavity is the leading cause of dental caries. Liang *et al.* [18] evaluated the antibacterial effect of hematoporphyrin monomethyl ether (HMME) and methylene blue (MB) with the different PS-light combinations on S. mutans biofilm and resulted that MB-aPDT could be an appropriate tool instead of HMME-aPDT for the plaque biofilm.

The clinical signs of peri-implantitis, an inflammatory pathological state of the body that affects the hard and soft tissues around dental implants, primarily affect the alveolar bone and peripheral gingival soft tissues. PDT for treating peri-implantitis also has apparent benefits for periodontal pathogenic bacteria [19]. Based on Caccianiga *et al.* [20] study, photodynamic therapy was better at diminishing trauma and pain while healing inflammation. After six months of treatment of peri-implantitis with PDT, the

periodontitis, infection detection depth, and frequency of bleeding, with high bacteria load were reduced [21].

The most prevalent form of periodontal disease, chronic periodontitis, is linked to a persistent buildup of bacterial plaque. Physical debridement should be followed by the administration of local/systemic antibiotics because mechanical procedures alone are insufficient for the treatment. Alternative therapies, including PDT, have resulted from these medications' adverse or side effects, such as bacterial resistance and patient allergies.

B. MEDICAL APPLICATIONS

PDT is an attractive alternative approach as an antibiotherapy for photoinactivation of a wide spectrum of pathogens, either Gram (+) or Gram (-), fungi, parasites, and viruses responsible for diverse illnesses in humans [22]. The effectivity of aPDT in the framework of inhibition of pathogens has been tested on many experimental parameters due to the development of resistance to commonly used antibiotics that are expected to be effective. Halili *et al*. [23] assessed the methicillin-resistant *Staphylococcus aureus* (MRSA) isolates' susceptibility to inhibition by rose bengal and riboflavin-mediated photodynamic treatment *in vitro*. Two multidrug-resistant MRSA bacteria were completely inhibited from growing *in vitro* by PDT mediated by rose bengal and riboflavin. It is considered crucial for treating bacterial keratitis caused by MRSA, which scars the cornea and impairs its functionality. Ma *et al.* [24] investigated the photodynamic effects on both azole-sensitive and azole-resistant *Candida albicans in vitro* using aloe-emodin (AE), a natural photosensitizer derived from *Aloe vera* and *Rheum palmatum*. It was demonstrated that AE is a viable PS for use in PDT of *Candida albicans* strains resistant to antibiotics, and AE-mediated PDT exhibits promising antifungal results. It is of great vitality that such studies for the future resistant strain crisis accelerate and are designed on a large scale.

Leg ulcers (LUs) are painful, debilitating, resistant to antibiotics, and impair the patient's quality of life standard. Krupka *et al.,* [25] PDT effectively treated patients with infected chronic LUs. 20 patients were divided into two experimental groups at random and given either 5-aminolevulinic acid photodynamic treatment or local octenidine dihydrochloride (octenilin gel) exposed to a placebo light source with an inserted filter that simulated red light (ALA-PDT). 8 months later, eight patients in the PDT group had had full remission (CR), eight had undergone partial response (>50% reductions in ulcer width), and two (20%) had not.

From a viral point of view, herpes simplex virus (HSV) is mostly responsible for oral and perioral herpetic lesions. Monjo *et al.* mentioned that the use of botanical plant essence orthokine compounds extracted from *Polygonum cuspidatum* and LEDs were significantly effective against HSV they thought that this effect might be due to damage to viral binding proteins [26]. Namvar *et al.* [27] compared the effects of PDT with a diode laser and/or indocyanine green (ICG) on HSV1 again and found that ICG alone had no discernible effect on viral CFU reduction. In this regard, it is difficult for the photosensitizer to have a significant toxic effect or to be the basis for inactivation without light exposure. Furthermore, coronavirus, another virus that has taken place most frequently on our agenda in recent years, was a target for Almeida *et al.* [28]. They proposed that COVID-19 may be reduced using photodynamic therapy employing well-known, secure, and affordable photosensitizers, such as methylene blue or protoporphyrin-IX, to treat infected patients, create useful photoactive textiles, auto-disinfect surfaces, or purify water and air. Against another important virus, papillomavirus, which is the cause of approximately 5% of cancers worldwide, Ambreen et al. [29] stated that photodynamic therapy with curcumin increases cell death, inhibits cell growth, and reduces colony formation and cell migration in papillomavirus-associated tumor cell lines.

IV. FOOD INDUSTRY PRACTICES OF PDT

In recent years, the accelerating researches on the implementation of PDT to in the agri-food field contribute to new knowledge on the inactivation of microorganisms, especially in food matrices. Therefore, the need for progressively prominent studies pointing out the use of aPDT in the food industry is increasing. According to a recent study concentrating on food safety, most studies that have been

published to date have been based mostly on research on the photodynamic inactivation of bacteria [30]. Considering that bacteria are the most common cause of foodborne illness [8], their predominance in the studies summarized in Table 1 is comprehensible.

Photosensitization holds promise for developing novel fruit and vegetable preservation methods [31] since it is a non-thermal, environmentally friendly, and cost-effective antibacterial treatment [32]. Therefore decontamination of fruit and vegetables is one of the most applied studies with different spoilage microorganisms or food-borne pathogens. Sheng *et al.* [33] conducted keystone research for the photosensitizing efficacy of vitamin K3 under UV-A, sunlight simulated and their antimicrobial activity against *Listeria monocytogenes* and *Escherichia coli* O157:H7 on lemon surfaces was investigated. On lemon surfaces, the combined antibacterial actions decreased *Listeria monocytogenes* and *Escherichia coli* O157:H7 by more than 5 log CFU/g and *Salmonella* Enteritidis by ~4 log CFU/g immediately following the treatment. Considering the share of *L. monocytogenes* in the morbidity and mortality of foodborne diseases and the causative agent of listeriosis, Huang *et al*. [34] elucidated the creation of antibacterial and antibiofilm blue light emitting diode PDT enhanced with 0.2 μM curcumin. Curcumin-supplemented PDT inactivated planktonic cells >4 log CFU/mL (99.99%) in 5 minutes even with a low dose (0.54 J/cm^2). Therefore, curcumin-mediated PDT has been recognized in the literature as a valid and non-thermal technique for inactivating planktonic and biofilm pathogens [35]. However, inactivation in complex food matrices instead of planktonic cells remains lower; therefore, suspension experimental designs will need to be carried forward. In one of the other encouraging studies, during a 15-minute exposure to xenon light, Cho and Ha [36] found that the cell counts of *E. coli* O157:H7, *Salmonella* Typhimurium, and *Listeria monocytogenes* diminished by 6.77, 2.74, and 6.43 log, respectively, without causing sublethal harm. The treated tomato juice samples' color, taste, pH, and lycopene concentration were assessed, but no appreciable changes were discovered. As this research shows, combined research on sensory and nutritional preservation strongly impacts the reality and feasibility of photodynamic therapy in food compositions.

Using thermal and chemical-based technologies for microbial control in the food sector frequently has a negative reputation called not environmentally friendly and can alter the finished goods' nutritional and organoleptic qualities. In addition, the effectiveness of sanitizing agents may decrease when microbial cells can develop biofilms. For this purpose, Silva *et al.* [37] searched the effect of PDT and the state of biofilms by using rose bengal and erythrosine with green LED against planktonic *Staphylococcus aureus*, *Enterococcus hirae*, *Escherichia coli*, and *Listeria innocua* in plants. Notably, the culturability of the biofilm cells decreased to undetectable levels, although higher concentrations of photosensitizers (0.01-50.0 μmol/L) had to be applied. Another opportunistic microorganism is *Pseudomonas aeruginosa*, one of the leading microorganisms that can form biofilms by adhering to food and food contact surfaces. Alam *et al.* [38] targeted the inactivation of ampicillin-resistance *P. aeruginosa* PAO1 but emphasized the inadequacy of using hypericin and orange light for the inactivation of the microorganism. It was found that using ampicillin and hypericin together, supported by orange light, 3.4 log reduced *P. aeruginosa*. However, it is thought that the preference of photodynamic therapy together with ampicillin, which is intended to replace it, might be used in the free-drug transition phase. In a decontamination study that offers a perspective where the surface area is changed, Yu *et al.* [39] evaluated the fresh-cut potato slices that were exposed to LED with 30 μM curcumin solution and as a result, *E. coli* and *S. aureus* were reduced by 2.43 and 3.18 log respectively. As a distinctive aspect of the study, PDT boosted phenylalanine ammonia-lyase activity while decreasing peroxidase and polyphenol oxidase activities, improving the overall antioxidant capacity with possible shelf life duration of the product, which is important for both dietary and waste aspects.
Polysaccharide, lipid, or protein-based edible package materials are getting more demand in the sustainability-focusing era so that in research about composite films was evaluated. When 1% CS-RB composite film was applied to a salmon with 5 log of the initial load, *L. monocytogenes* and *Shewanella baltica* were decreased by about 3 log and the cells of *Vibrio parahaemolyticus* were totally inactivated [40]. In another research on the solution of photodynamic therapy for another common foodborne disease factor in packed materials, Le *et al*. [41] developed a film based on poly (3-hydroxybutyrate-co-3-hydroxyvalate) combined with aloe-emodin under blue light and the performance of the material showed 4.7 log bactericidal activity against *E.coli*.

Table 1. *Food-borne diseases and spoilage-related microorganisms with their reductions with PDT.*

Type of Photosensitizer	Microorganism(s)	Source of light (Wavelength and Irradiance)	Fluence	Session duration	Substrate	Reduction	Reference
Riboflavin (5 μM)	*Escherichia coli* O157:H7	Blue LED light: 360-1100 nm -	30 J/cm^2	19 min 23s	Apple juice	3 log CFU/ml	[42]
	Salmonella Typhimurium					~4.3 log CFU/ml	
Curcumin (20μM)	*Escherichia coli* DH5α	Blue LED light: 470 nm 60 mW/cm^2	3.6 J/cm^2	60 s	Oyster	3.5 log CFU/g	[43]
-	*Salmonella* Agona *Salmonella* Newport *Salmonella* Saintpaul *Salmonella* Typhimurium	LED light: 405 ± 5 nm 10 ± 1 mW/cm^2	1.3-1.7 kJ/cm^2	36-48 h	Fresh-cut papaya	0.3-1.3 log CFU/g	[44]
Hypericin (1.5x 10^{5}M)	*Bacillus cereus*	LED light: 585 nm 3.84 mW/ cm^2	6.8 J/cm^2	30 min	Fruits and vegetables	4.4 log CFU/ml	[45]
Riboflavin (150 μmol/L)	*Salmonella* Typhimurium *Salmonella* Enteritidis	Blue LED light: 455 ± 5 nm 5.2 mW/cm^2	93.6 J/cm^2	-	Tuna	2.1 log CFU/ml	[46]

Curcumin (40 μM)	*Staphylococcus aureus*	LED light: 450 nm 55 mW/cm^2	15 J/cm^2	30 min	Beef	1.5 ± 0.2 log CFU/ml	[47]
					Chicken	1.4 ± 0.2 log CFU/ml	
					Pork	0.6 ± 0.4 log CFU/ml	
Curcumin (80 μM)			10 J/cm^2		Apple	2.0 ± 0.4 log CFU/ml	
Curcumin (200 μM)	*Klebsiella pneumoniae*	LED light: 430 ± 5 nm	150 J/cm^2	-	Bovine casing	2.7 ± 0.1 log CFU/ml	[48]
	Salmonella Typhimurium					3.8 ± 0.2 log CFU/ml	
Curcumin (10 μM)	*Staphylococcus aureus*	Blue LED light: 440 ± 5 nm 3.6×10^{-3} W/cm^2	2.592 J/cm^2	12 min	Mango juice	~5 log CFU/ml	[49]
					Pineapple juice		
CUR-D-Tyr co-crystal (5 μg/ml)	*Vibrio parahaemolyticus*	Blue LED light: 460 nm 40-45 mW/cm^2	-	20 min	Cooked clams	~2.3 log CFU/ml	[50]
Curcumin (5 μg/ml)						~1.7 log CFU/ml	

Curcumin (10 and 20 μM)	*Vibrio parahaemolyticus*	LED light: 470 nm 0.06 W/cm^2	3.6 J/cm^2	60 s	-	6.5 log CFU/ml	[51]
Curcumin (10 mg/L)	*Aeromonas hydrophila*	LED light: 470 nm 20-40 mW/cm^2 + UV-A light: 400 nm 18W	3.6 J/cm^2	15/30 min LED + 5/10 min UV-A	-	4 log CFU/ml	[52]
	Vibrio parahaemolyticus					6 log CFU/ml	
Curcumin (50 μmol/L)	*Vibrio parahaemolyticus*	Blue LED light: 460 nm	-	60 min	Fresh-cut Hami melons	~1.8 log CFU/g	[53]
Curcumin (300 mg/L)	*Listeria monocytogenes*	LED light: 430 nm 0.107 W/cm^2	32.1 kJ/m^2	5 min	Chicken	2.9 log CFU/cm^2	[54]
	Salmonella					1.5 log CFU/cm^2	
Curcumin (50 μM)	*Aspergillus flavus*	LED light: 420 nm	60 J/cm^2	-	Maize kernels	~3 log CFU/g	[55]
Curcumin (50 μM)	*Aspergillus flavus*	Xenon arc lamp machine: 350-650 nm 118.71 mW/cm^2	114.5 J/cm^2	15 min	Peanuts	1.7 log CFU/ml	[56]
Curcumin (25 μM)	*Staphylococcus saprophyticus*	Blue LED light: 430-470 nm 7.2 mW/cm^2	4.32 J/cm²	10 min	Fresh dough sheet	~5 log CFU/ml	[57]

Curcumin (50 μM) + 0.4% (w/v) EDTA	*Burkholderia cepacia*	Blue LED light: 425 nm 16 mW/cm^2	-	30 min	-	~4 log	[58]
-	*Escherichia coli*	LED light: 405nm	-	60 min	UHT sterilized skim milk	4.69 log CFU/ml	[59]
Curcumin (100 μM)	Total bacteria count	LED light: 410 nm	-	10 min	Fresh-cut pineapple	1.11 log	[60]
Curcumin (2 μmol/L)	*Escherichia coli*	LED light: 420 nm 298 mW/cm^2	-	510 s	Fresh-cut apple slices	0.95 log	[61]
Chlorophyllin (1×10^{-5} mol/L)	*Pseudomonas* spp.	LED light: 405 nm 5.1 W/m^2	44.54 J/cm^2	24 h	Fresh-cut Pakchoi	0.1-0.7 log	[62]

Methylene blue (10 μM) + Potassium iodide (100 μM)	Spores of *Alicyclobacillus acidoterrestris*	White LED light: 400-700 nm 140 mW/cm^2	-	10 h	UHT orange juice	5 log CFU/ml	[63]
Eosin Y (10 μmol/L)	*Pseudomonas aeruginosa*	Green LED light: 490-570 nm 10 mW/cm^2	106.2 J/cm^2	10 min	-	1-2.5 log CFU/ml	[64]
Quercetin (75 μM)	*Escherichia coli* O157:H7	Blue LED light: 405 nm 19.5 mW/cm^2	80 J/cm^2	68 min 21s	-	4 log CFU/ml	[65]
	Listeria monocytogenes					6 log CFU/ml	

V. CONCLUSION & FUTURE DIRECTIONS

Developing effective and reliable aPDT practices requires specialist knowledge in various research areas, including physics, chemistry, and biology, with the disciplines of engineering due to creating a defense mechanism against microorganisms. The increasing volume and deepening intensity of interdisciplinary studies about PDT fortify the potential for aPDT to transform into a routine sterilization technology for the food industry. However, due to the complex microbial flora, and multi-layered and shelf-life-dependent nature of food matrices, further studies are needed for commercialization and large-scale adoption. At this point, the system parameters that will be determined by the cooperation of academia and industry specifications for each food target will be decisive. Besides, aPDT will be a more promising method if it will be part of a hurdle approach with non-thermal novel technologies like PEF and ultrasound. The selection of natural photosensitizers such as curcumin, preferred from the consumer perspective is also a positive choice for catching up with the current green trends and providing sustainability for the technique. Finally, accelerated stability tests to ensure food safety might be an essential part of the main target.

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