

Table 2. Cont.

Merchat <i>et al.</i> , 1996 [263]	<i>Vibrio anguillarum</i> <i>E. coli</i> <i>Enterococcus seriolicida</i>	Two <i>meso</i> -substituted cationic porphyrins: tetra(4N-methylpyridyl)porphine tetraiodide and tetra(4N,N,N-trimethyl-anilinium)porphine, and negatively charged <i>meso</i> -substituted porphyrin, tetra(4-sulphonatophenyl)porphine	10 $\mu\text{g mL}^{-1}$	0-30 minutes	White light (four 250 W tungsten lamps)		6 mW cm^{-2}	10 ⁸ CFU mL^{-1}
Merchat <i>et al.</i> (b), 1996 [264]	<i>Vibrio anguillarum</i> <i>E. coli</i> <i>Enterococcus seriolicida</i>	<i>meso</i> -tetra (4-N-methylpyridyl)porphine tetraiodide, T4(4-N-MePy)P; <i>meso</i> -tetra (3-N-methylpyridyl)porphine tetrachloride, 1"4(3-N-MePy) P; tri(4-N-methylpyridyl)monophenylporphine Iritosylate, T3(4-N-MePy) PhP; di(N-methyl-4-pyridyl)diphenylporphine dichloride (D(4-N-MePy) Ph2P	8.4 μM	0-30 minutes	White light (250 W quartz-tungsten lamps)		6 mW cm^{-2}	
Nitzan and Ashkenazi, 2001 [266]	<i>Acinetobacter baumannii</i> and <i>Escherichia coli</i> B	Cationic TMPyP	29.4 mmol L^{-1} (p), 3.7 mmol L^{-1} (j), 1.83 mmol L^{-1} (F), and 0.73 mmol L^{-1} (h)		Blue, green and red light		140-150 mW cm^{-2}	10 ⁹ CFU mL^{-1}
Nitzan <i>et al.</i> , 1998 [269]	<i>Acinetobacter baumannii</i>	Deuteroporphyrin (Dp) and polymyxin nonapeptide (PMNP) ; Cd-texaphyrin (Cd-Tx) in the presence of PMNP; cationic photosensitizer tetramethylpyridyl porphine (TMPyP); anionic photosensitizer tetra-sulfonatophenyl porphine (TPPS4)	Deuteroporphyrin (Dp) at a concentration of 34 μM and polymyxin nonapeptide (PMNP) at a concentration of 200 μM	0-210 minutes	White light (unfiltered tungsten lamps)		140 W m^{-2}	10 ⁸ CFU mL^{-1}
Oliveira <i>et al.</i> , 2009 [267]	<i>Bacillus cereus</i> endospores and vegetative cells	Neutral and cationic porphyrin derivatives, and phenothiazinium dye toluidine blue O and 10,15,20-tris(1-methylpyridinium-4-yl)-5-(phenyl)porphyrin tri-iodide (Tri-Py+-Me-Ph, tricationic	10 and 60 μM	4 and 10 minutes for endospores and for 15 minutes for vegetative cells	White light (400-800 nm)	152.1 J cm^{-2} (maximum dose)	1690 W m^{-2}	10 ⁶ -10 ⁷ CFU mL^{-1}

Table 2. Cont.

Spesia <i>et al.</i> , 2005 [235]	<i>E. coli</i>	Meso-substituted cationic porphyrins, 5-[4-(trimethylammonium)phenyl]-10,15,20-tris(2,4,6-trimethoxyphenyl)porphyrin iodide 1, 5,10-di(4-methylphenyl)-15,20-di(4-trimethylammoniumphenyl)porphyrin iodide 2 and 5-(4-trifluorophenyl)-10,15,20-tris(4-trimethylammoniumphenyl)porphyrin iodide 3	10 μ M	5 minutes	Visible light		0.68, 2.60 and 90 mW cm^{-2}	10^6 CFU mL^{-1}
Tang <i>et al.</i> , 2007 [268]	<i>S. aureus</i> (ATCC 25923), <i>E. coli</i> (ATCC 25922), a clinical isolate of MRSA, and a clinical isolate of ESBL-producing <i>E. coli</i>	Toluidine blue O and poly-l-lysine chlorin(e6) conjugate (pL-ce6)	4-8 μ M	30 minutes	Red light	10-30 J cm^{-2}	400 W	10^8 CFU mL^{-1}
Wainwright <i>et al.</i> , 1998 [204]	MRSA strains	Phenothiazinium dyes						
Wilson and Yianni, 1995 [244]	MRSA strain	Toluidine blue	1.6-12.5 $\mu\text{g mL}^{-1}$	1 minute	Low power helium/neon laser	0.5-2.1 J cm^{-2}	35 mW	10^{10} CFU mL^{-1}

3.4. Photodynamic Antimicrobial Therapy Application in Fish Farm Plants

Although just a few studies have been conducted in this field (Table 2), preliminary results obtained at both laboratory level and pilot station suggest that the photochemical technique, using porphyrin derivatives as PS, has a great potential also for the disinfection of fish farming plant waters [100,290]. These studies showed that cell cultures of Gram-positive bacteria (e.g., methicillin-resistant *S. aureus*), Gram-negative bacteria (e.g., *E. coli*), fungal (e.g., *C. albicans*) and fungal-like pathogens (e.g., *Saprolegnia* spp.) and parasitic protozoa (e.g., *Acanthamoeba palestinensis*) showed a 5-6 log decrease in the microbial population after 10 minutes of irradiation with low light intensities (ca. 50 mW cm^{-2}) in the presence of micromolar PS doses [290]. Magaraggia *et al.* have also shown that a micromolar concentration of a porphyrinic PS promoted the cure of saprolegniosis in trout-farming pools containing naturally or artificially *Saprolegnia* infected fish (inactivation of 6-7 logs) without perilesional damage of the fish. A stock of fish were transferred to a 1,000 L tank and, after acclimatization, skin fish was infected by scraping dorsal trout epidermis and inoculated with *Saprolegnia* by direct contact of the lesions with mycelium wads. The infected group was dark incubated with 0.6 mg L^{-1} for 10 min in an 80-150 L pool and irradiated for 1 h kept in a closed circuit and recirculated by a motor-driven pump. The irradiation was performed by using the 400-800 nm wavelength interval emitted from two 100 W incandescent filament lamps and the water temperature was kept at 13 °C throughout the light exposure. The treatment was daily repeated for six consecutive

days. After each treatment repetition, fish were moved to a 1,000 L tank. The onset of the infection in healthy fish was reduced about 50%. Recurrence of the saprolegniosis in the *Saprolegnia* infected sites or in others sites of the fish was not observed. The trout set with spontaneous infection by *Saprolegnia* a complete remission of the infection was induced within one week. The same micromolar concentrations exhibited also higher photosensitizing activity over meticillin-resistant *S. aureus* and *E. coli* (up 7 logs decrease) [100]. The antimicrobial effects of PDT were also demonstrated for *V. vulnificus* that frequently infects fish farming water [291]. Similarly, ten bacterial species (*V. anguillarum*, *V. parahaemolyticus*, *Photobacterium damsela* subsp. *damsela*, *Photobacterium damsela* subsp. *piscicida*, *A. salmonicida*, *E. coli*, *Enterobacter*, *S. aureus*, *E. faecalis*, *Pseudomonas* sp.) isolated from a fish farming plant waters were effectively inactivated (up to 7 logs) *in vitro* with cationic porphyrins, at micromolar PS doses, after 90-270 minutes of irradiation with a very low light intensity of 4 mW cm⁻² [292], showing that photodynamic therapy can be used to photoinactivate fish bacterial pathogens in fish farm waters even during dark days of winter time. In these experiments fifty milliliters of bacterial suspensions from bacterial cultures (~10⁸ cells mL⁻¹) were diluted ten-fold in phosphate buffered saline to a final concentration of ~10⁷ colony forming units mL⁻¹ and exposed, in 600 mL glass beakers, to the PS under the white light. Bacterial inactivation was evaluated by counting the number of colonies, by pour plating method, in the exposed samples.

Irradiation of fish farming waters by solar light, which penetrates deeply into the water column, thereby allowing the uniform illumination of large volumes [293] makes this technology inexpensive since it is based on the use of low cost visible light sources.

The promising results of PACT on a large range of microorganisms, Gram-positive and Gram-negative bacteria including multidrug-resistant strains, bacterial spores, virus, bacteriophages, yeasts and helminths eggs [233,243,255,256,267,273,274,276,279,294-299] and the knowledge that the porphyrins' mode of action make the selection of photoresistant strains very unlikely [237,300], suggest that this principle can be applied to photodecontamination of fish farming plants, in order to destroy pathogenic microorganisms. To implement this technology in fish farming plants some studies will be need to be carried out, namely pertaining to the determination of the stability of the new hybrid-porphyrin conjugates under visible light irradiation conditions. Moreover, there are no studies on the impact that this procedure might have on the total microbial community structure after treatment.

3.5. Advantages of Photodynamic Antimicrobial Chemotherapy over other Treatments in the Environment

The main favorable aspects of PACT for environmental use are the following [44,251]: (1) a broad spectrum of action: the PS inactivates efficiently bacteria, viruses, fungi, and parasites in both the dormant and vegetative states contrarily to chemotherapy and phage therapy; (2) an efficient phototoxic activity against both wild and antibiotic-resistant microbial strains; (3) the lack of selection of photoresistant microbial species; (4) a low mutagenic potential; (5) a high selectivity in the killing of pathogens as compared with the main constituents of potential host tissues; (6) a high selectivity in space and time: the microsecond short lifetime and high reactivity of singlet oxygen (the main pathway of PACT inactivation), restricts the photooxidative damage to the microenvironment of the site where

it is generated to about 0.1 μm [194,195]; (7) the lack of generation of potentially dangerous or toxic by-products from photoinduced degradation of the photosensitizing agent; (8) cost-effective technology, as it is based on the use of visible light sources, as solar irradiation; (9) the possibility to reuse the immobilized PS which makes this technology less expensive and avoids its diffusion to the environment, preventing any risk of environmental contamination.

Conclusions

The possibility to inactivate fish pathogenic microorganisms with phages and/or immobilized photosensitizers is outstanding, being the major advantage the efficient water disinfection degree obtained without risk to fishes or to the environment. The safety of the photodynamic therapy approach is increased as porphyrin derivatives apparently do not induce the selection of resistant microbial strains. Although, in some cases, phage therapy approach can lead to the selection of resistant bacteria, its occurrence and impact is not as so frequent and harmful as antibiotics chemotherapy.

The new approaches described in this review are intrinsically low cost compared to the chemical compound normally used in aquaculture systems and are conceived to be environmentally-friendly and to exhibit a high level of safety for various ecosystems, as well as for humans, animals and plants.

More studies are needed in order to gather a detailed understanding of phage-bacterium and of photosensitizer-microorganisms interactions in aquaculture systems subjected to different environmental pressure. A better understanding of phage therapy and of photodynamic therapy as adjuvant use of antibiotics and/or other disinfectant in fish farming plants also need to be further studied.

Each of the two techniques has its advantages but also its limitations. The application of phage and of photodynamic therapies must be based on a careful evaluation of each case, before replacing conventional approaches. Nevertheless, a good biocontrol management strategy might be the use of more than one technique in rotation to prevent resistance development. Alternatively, it might be valuable to apply both techniques to maximize protection against pathogenic microorganisms.

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