

## Advances in Photodynamic Antimicrobial Chemotherapy

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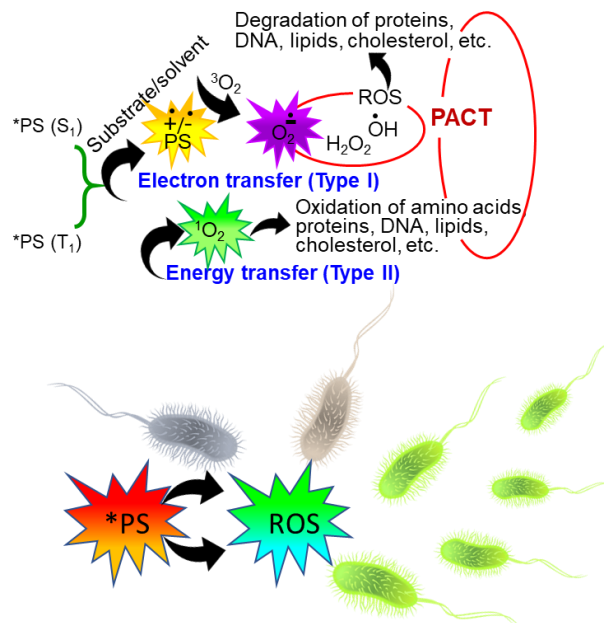
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### Abstract

Photodynamic therapy (PDT) and photodynamic antimicrobial chemotherapy (PACT) combine light and photosensitizers to treat cancers and microbial infections, respectively. In PACT, the excitation of a photosensitizer drug with appropriate light generates reactive oxygen species (ROS) that kill pathogens in the proximity of the drug. PACT has considerably advanced with new light sources, biocompatible photosensitizers, bioconjugate methods, and efficient ROS production. The PACT technology has evolved to compete with or replace antibiotics, reducing the burden of antibiotic resistance. This review updates recent advances in PACT, with special references to light sources, photosensitizers, and emerging applications to microbial infestations. We also discuss PACT applied to COVID-19 causing SARS-CoV-2 treatment and disinfecting food materials and water. Finally, we discuss the pathogen selectivity and efficiency of PACT.

**Keywords:** *PACT, photodynamic therapy, antimicrobial, bacteria, fungus, COVID-19*

## TOC Graphic



## Introduction

Recent advancements in photodynamic therapy (PDT) have underlined its potentials in antimicrobial chemotherapy to replace antibiotics from various human, veterinary, and aquaculture medicine sectors. Also, the principles of PDT are applied to disinfect water and treat wastewater. For over a century, the non-judicial use of antibiotics has resulted in the emergence of antibiotic-resistant bacteria [1], a global health peril recorded by WHO, estimated to cause 10 million human deaths annually by 2050 [2]. In photodynamic antimicrobial chemotherapy (PACT), an infected area is exposed to a combination of light and a photosensitizer (PS) drug, where the PS replaces antibiotics. PACT is envisaged to kill microorganisms through the photosensitized production of reactive oxygen species (ROS). PACT is refined for selectively killing bacteria over mammalian cells [3], intracellular imaging, and photo-inactivation [4].

The PDT concept was introduced in the early 1960s, and subsequently, it progressed to clinical trials, and currently, PDT protocols are available for treating many types of cancers [5-11]. The present status of the clinical adoption of PDT for various cancers is reviewed recently by Li *et. al.* [12]. The advantage of PDT is that it is highly controllable and can be combined with other treatment modalities, such as chemotherapy, immunotherapy, gene therapy, and radiotherapy [13, 14]. Recent studies reported several ways to improve the oxygen concentration in hypoxic tumor microenvironments to

increase PDT efficacy. The PS decorated on photosynthetic cyanobacteria performs the dual purpose of oxygenating the hypoxic tumor cells and ROS generation [15, 16].

Though PDT was developed from observing endogenous porphyrin fluorescence during surgery, the use of PSs for microbial eradication traces back to before the age of chemotherapy [17]. The ancient version of phototherapy is heliotherapy, where various diseases were treated by exposure to sunlight alone or in combination with plant pigments [18]. According to Wainwright, the combination of a dye and a light source for antimicrobial treatment should be called PACT [17]. Paul Ehrlich formulated the photodynamic action principles after decades of aniline dyes staining experiments on animals and microbes. It means a live microbe can be killed by light illumination if selectively stained with a vital dye. Hermann von Tappeiner, based on the studies of Oscar Raab, introduced the term *photodynamic* in 1904 to describe oxygen-dependent chemical reactions induced by photosensitization [19]. The studies had shown that the combined action of light and a drug acridine orange killed *Paramecia* efficiently. Further, Tappeiner and colleagues contended that these photobiological reactions are highly dynamic and distinguished from photosensitization. Hence, the term photodynamic reaction was coined for all photobiological reactions occurring in the presence of oxygen. We review the current status of PDT in controlling microbial pathogens and its potential applications in curing bacterial, viral, and fungal pathogens in humans and animals. Also, we evaluate the prospects of photodynamic action for disinfecting water and treating wastewater.

### **Advantages of PACT**

While PACT to treat infections is still in its infancy, there are many significant advantages. It is a low-cost technique compared to the chemicals usually used. It is conceived to be environmentally friendly and exhibits a high safety level for various applications. The main advantages of PACT are the following [3, 20-25]. (1) A broad spectrum of action: PSs efficiently inactivate bacteria, viruses, fungi, and parasites in both dormant and vegetative states contrary to chemotherapy, (2) an efficient phototoxic activity against both wild and antibiotic-resistant microbial strains, (3) lack of selection of photo-resistant microbial species, (4) a low mutagenic potential, (5) a high selectivity in the killing of pathogens as compared with the host tissues, (6) a high selectivity in space and time; the microsecond short lifetime and high reactivity of singlet oxygen ( $^1\text{O}_2$ ) restrict the photooxidative damage to the microenvironment, and (7) the possibility to reuse a PS, making the technology less expensive and environmentally friendly. However, the reactive oxygen species (ROS) generated on photoexcitation are nonspecific, and therefore they may kill both the pathogenic and beneficial bacteria in the

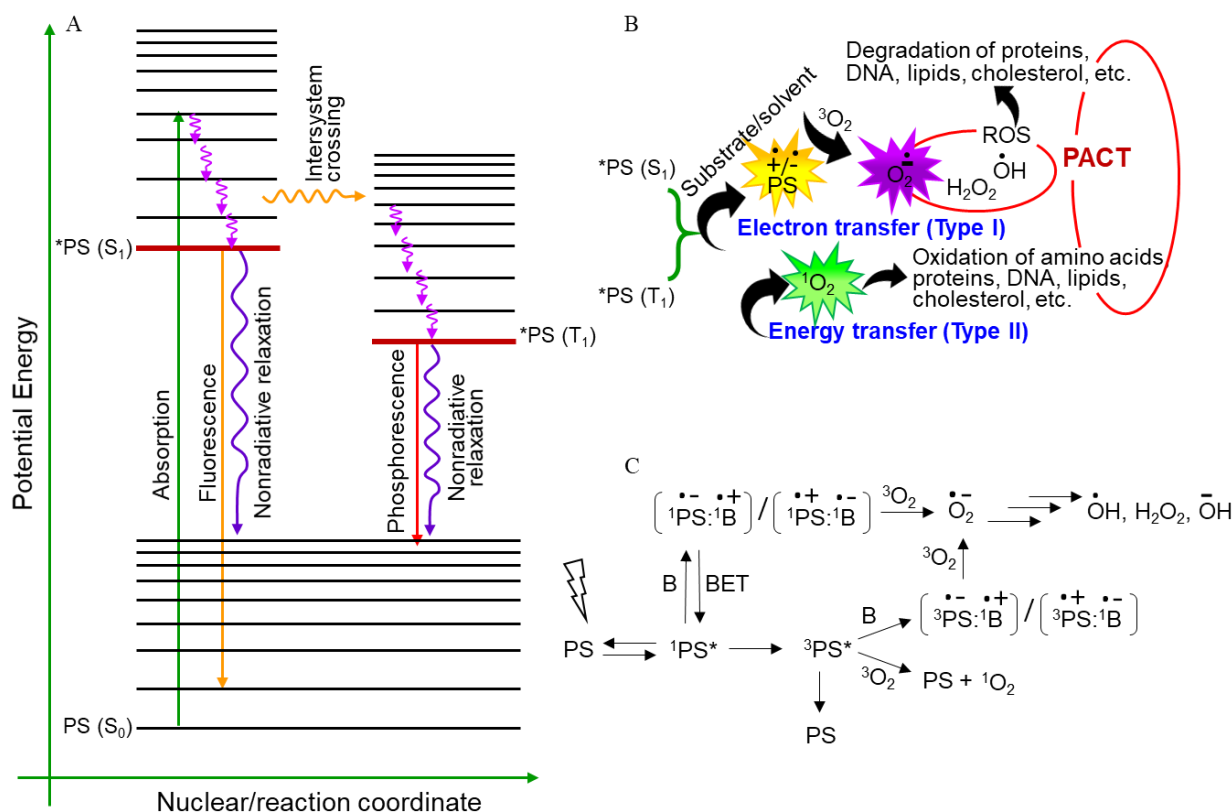
proximity. Suppose the concentrations of ROS are above the tolerable limits of host organisms. In that case, these species also induce unintentional effects such as killing the host cells. The current technologies permit us to control the reaction by optimizing the PS concentrations, light/chemical exposure time, and light intensity. Statistical models such as the response surface methodology were also used [26]. However, advances in the organism-specific attachment/delivery of PSs and controlled production/release of ROS are challenging.

PACT effectively kills *Escherichia coli* and *Pseudomonas aeruginosa*; organisms responsible for infections in animals [27]. A first-generation PS such as toluidine blue or methylene blue induces cell wall damage and DNA breakage in the target microorganisms. Furthermore, the potencies of some virulence factors (lipopolysaccharides and protease) have been shown to decrease by photosensitization [27]. Due to the localized and noninvasive nature, many antibiotics' side effects are unlikely to occur with PACT. Furthermore, the development of resistance to PACT would be unlikely since its bactericidal activity is due to  $^1\text{O}_2$  and other ROS such as hydroxyl radicals, which affect a range of cellular targets. Viruses like HIV-1, HSV, and VSV are also amenable to the ROS generated by PSs. For example, methylene blue photodamages the core proteins, viral RNA, and enzymes of HIV-1 [28]. A recent outbreak of COVID-19 also promoted photodynamic action in self-sanitizing masks and supporting materials for the health workers and public.

## **The principles and components of PDT**

### **Type I and Type II mechanisms**

PDT has been investigated extensively at the *in vivo*, cellular and molecular levels. The three major components of PDT are a light source, a PS, and oxygen. In a photodynamic reaction, photon absorption by a PS creates its electronically excited singlet state ( $S_1$ , Figure 1A). An excited



**Figure 1.** (A) A scheme of photosensitization in PACT. (B) Type I and Type II reactions following photosensitization. (C) ROS generation in PDT and PACT. B in (C) is the substrate or a biomolecule that acts as an electron donor/acceptor.

relaxes radiatively or nonradiatively to the ground singlet state ( $S_0$ ), undergoes electron transfer to a target molecule in a biological substrate (Figure 1B), or generates a long-lived triplet excited state ( $T_1$ ) by intersystem crossing. As discussed in the following section, an electron transfer from the  $S_1$  state to a biomolecule is not a dominant photodynamic therapy pathway. Although triplet-triplet energy transfer to oxygen dominates the photodynamic pathway of the  $T_1$  state, leading to  $^1O_2$  generation, electron transfer is also operative in this state. The excited-state processes in the  $S_1$  and  $T_1$  states eventually produce ROS (Figure 1C), such as superoxide ( $O_2^{\bullet-}$ ), hydrogen peroxide ( $H_2O_2$ ), hydroxyl radical ( $HO^{\bullet}$ ), and  $^1O_2$ . The photophysical processes and chemical reactions involving electron transfer in the  $S_1$  and  $T_1$  states and energy transfer in the  $T_1$  state are grouped under the Type I and Type II mechanisms (Figure 1B).

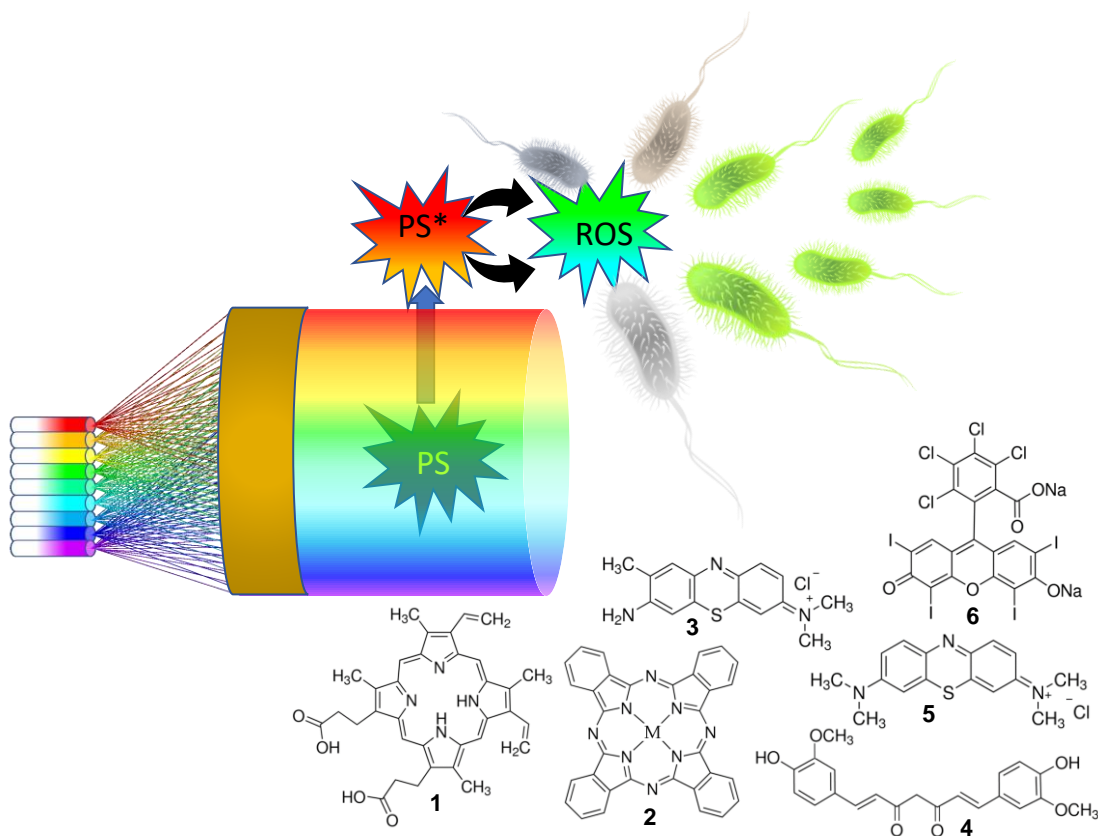
The fundamental process in the Type I mechanism is an electron transfer from a singlet or triplet excited PS to a biomolecule or a solvent molecule. A photoexcited PS in the  $S_1$  or  $T_1$  state is more oxidizing or reducing than its ground state. An unpaired electron in the lowest unoccupied molecular orbital (LUMO) of the excited state PS becomes the donor (reducing species). In contrast, a hole in the

highest occupied molecular orbital (HOMO) becomes the acceptor (oxidizing species) in the  $S_1$  or  $T_1$  state. The redox potentials of a photoexcited PS or the free energy change of an electron transfer from or to the excited state can be calculated by combining Balzani equations [29] with the Rehm-Weller equation [30]. Let's consider a PS in the  $S_1$  state, which forms a collision complex called an exciplex, with an electron acceptor/donor. The acceptor/donor can be a biomolecule or a solvent molecule. Here, the exciplex prefers back electron transfer (BET) to form the corresponding ground states but not an electron transfer to form the radical ions. This preference is intrinsic to the spin-allowed, rapid, exothermic BET process. Conversely, the encounter complex takes the triplet character when a PS in the  $T_1$  state interacts with a singlet acceptor/donor. Thus, unless the hyperfine or spin-orbit coupling breaks the multiplicity of the intermediate, the BET process becomes spin forbidden, preferring charge separation to form radical ions. Also, the radical ion pairs are stabilized in the physiological medium with a high dielectric constant, enabling their escape from the solvent shell. Such radical ions trigger a series of processes involving electron transfer or hydrogen abstraction reactions. A PS or a substrate radical anion interacts with oxygen to form superoxide and then a chain of ROS such as  $OH^\bullet$ ,  $OH^-$ , and  $H_2O_2$ . Among these,  $OH^\bullet$  is the most reactive. Thus, the Type I mechanism is preferred in PACT. For example, porphyrins and phthalocyanines produce superoxide and follow the Type I pathway in the highly polar cytoplasm; the formed PS radical ions and ROS damage various substrate biomolecules and solvents. Proteins, amino acids, lipids, and nucleic acids with phenolic, hydroxyl, amino, ene, or quinone structures are susceptible to radical ions or ROS to trigger a series of Type I reactions, eventually cross-linking and damaging biomolecules and subcellular organelles [31-33].

In the Type II mechanism, a PS with a long-lived triplet state transfers a part of its energy to the ground state oxygen ( $^3O_2$ ,  $^3\Sigma_g^- O_2$ ) through triplet-triplet annihilation, producing  $^1O_2$ . The formed  $^1O_2$  has two states,  $^1\Sigma_g^+$  and  $^1\Delta_g$ , where the short-lived  $^1\Sigma_g^+ O_2$  readily relaxes to the stable  $^1\Delta_g O_2$  state. The significance of  $^1O_2$  as a cytotoxic species to PDT and PACT has emerged since the first demonstration of dye-sensitized  $^1O_2$  generation [34]. Indeed, the reaction mechanism of  $^1\Delta_g O_2$  in PDT was realized by the photosensitized generation of  $^1O_2$  using hematoporphyrin or a phthalocyanine derivative to oxidize cholesterol.  $^1O_2$  induces cell death in PDT and PACT by interacting with and damaging biomolecules in the mitochondria, nucleus, cell membrane, etc. Nevertheless, the lifetime of  $^1\Delta_g O_2$  is an important parameter in this PDT/PACT route. Although  $^1\Delta_g O_2$  is long-lived ( $\gg 3 \mu s$ ) in an organic solvent, it is deactivated within  $3 \mu s$  in water,  $0.1 ms$  in lipid membranes, and  $0.25 \mu s$  in a physiological environment. Despite the longer lifetime of  $^1\Delta_g O_2$  in the cytoplasm, stable radical ions force the Type

I pathway in subcellular polar pockets. Thus,  $^1\Delta_g \text{O}_2$  pathways are preferred in lipid membranes where the hydrophobicity does not stabilize the radical ions. Nevertheless, high concentrations of electron acceptors or donors are prerequisites for the Type I pathway unless a charge transfer complex is not formed. Conversely, the diffusion range of  $^1\Delta_g \text{O}_2$  is limited to ca 45 nm in PDT/PACT, relative to the PS [25]. Thus, PDT or PACT efficiency becomes significant when a PS closely interacts with a cell/microbial organelle such as the mitochondrion, where the  $\text{O}_2$  formed immediately reacts with biomolecules. Thus, a PS drug in the intracellular compartment is more efficient than in the extracellular matrix, underscoring the significance of combining PDT or PACT with PS drug delivery for higher therapeutic efficiencies.

Even though ROS generation is by the above electron or energy transfer processes, it is still challenging to determine the reaction mechanisms in a biological system. However, we can speculate the path based on the reaction products and whether a biomolecule/solvent/substrate or oxygen interacts with the excited PS. As stated above, the lifetimes or stabilities of the intermediates (a PS radical ion in the Type I mechanism, or  $^1\text{O}_2$  in the Type II mechanism) and biological environment (a lipid domain or a polar pocket) of a PS determine the phototherapeutic pathway. Also, at higher oxygen concentrations,  $^3\Sigma_g^- \text{O}_2$  efficiently complexes with a triplet excited PS, forcing the energy transfer pathway to produce  $^1\Delta_g \text{O}_2$ ; whereas PDT/PACT reactions proceed through the Type 1 pathway under the hypoxic condition.



**Figure 2.** A scheme of the three major components (light, PS, and ROS) for a successful photodynamic reaction. **(1-6)** The structures of common PSs in PACT: **(1)** chlorine e6, **(2)** metal phthalocyanine, **(3)** toluidine blue O, **(4)** curcumin, **(5)** methylene blue, **(6)** Rose Bengal.

Figure 2 shows the structures of common PSs in PACT. The Type II mechanism is preferred for PDT and PACT as the direct electron/hydrogen transfer in the type I pathway eventually damages the PS. The success of PACT is attributed to many factors like cell structure and organization, the physiological state or type of an organism, dosage and physicochemical properties of the PS applied,  $^1\text{O}_2$ , and the location of PS delivery and activation. Also, the power and wavelength of the light source and the exposure time contribute to the PACT efficiency.

The key step in PACT is the generation of  $^1\text{O}_2$  by a PS upon excitation.  $^1\text{O}_2$  is a reactive form of molecular oxygen and can react with a variety of biologically important entities. Despite being discovered in 1924,  $^1\text{O}_2$  became the focus of intense studies after 1963 when Khan and Kasha interpreted the hypochlorite–peroxide chemiluminescence caused by  $^1\text{O}_2$  [35].  $^1\text{O}_2$  is involved in several biological processes such as photooxidation of xenobiotics, lipids, and enzymes. The molecular oxygen exhibits an unusual paramagnetic behavior with the ground triplet state. In this state, molecular oxygen has two unpaired electrons with parallel spins in the two degenerate anti-bonding orbitals



giving the spin multiplicity 3. In PDT/PACT, a PS is excited to its singlet state with the energy of ~ 170-190 kJ mol<sup>-1</sup>. This energy corresponds to a wavelength in the 620-690 nm range. After the intersystem crossing, a triplet PS with the energy of 110-130 kJ mol<sup>-1</sup> is created. This molecule transfers its energy to oxygen, producing <sup>1</sup>O<sub>2</sub> with the energy of ~ 94.5 kJ mol<sup>-1</sup>. Lee and Rodgers [36] analyzed the reactivity of <sup>1</sup>O<sub>2</sub> generated by the photoactivation of Rose Bengal and found a significant reactivity only to guanosine. Devasagayam *et. al.* found that <sup>1</sup>O<sub>2</sub> oxidizes guanine nucleosides leading to the formation of 8-oxo-7-hydrodeoxyguanosine [37]. The lifetime of <sup>1</sup>O<sub>2</sub> in cellular systems ranges from 100 ns in the lipid region of the membrane to 250 ns in the cytoplasm. By considering the average <sup>1</sup>O<sub>2</sub> diffusion range in a cell to be ca. 45 nm and the diameters of human cells from 10 to 100 μm, <sup>1</sup>O<sub>2</sub> produced within a cell cannot diffuse outside [38]. The oxygen concentration in the environment surrounding the bacteria is important for the photodynamic killing of the bacteria because oxygen is consumed during the peroxidation of cellular constituents. Thus, the oxygen concentration can be depleted, and as a result, the <sup>1</sup>O<sub>2</sub> quantum yield decreases. <sup>1</sup>O<sub>2</sub> itself is a cytotoxic agent, at least to microorganisms, which was proved experimentally where the PS did not interact with the cell membrane or penetrate the cytoplasm. Each PS can typically produce 10<sup>3</sup>-10<sup>5</sup> <sup>1</sup>O<sub>2</sub> molecules before undergoing degradation by photobleaching. Recent studies indicated that the addition of potassium iodide (KI) dramatically improves the PACT efficiency up to a million times [39-41]. This enhanced bacterial killing was attributed to the production of H<sub>2</sub>O<sub>2</sub> [39, 40] by two possible reasons for exciting a combination of a PS and KI [39]. First, the <sup>1</sup>O<sub>2</sub> produced during photosensitization might receive one electron from iodine to produce superoxide, which undergoes dismutation to give H<sub>2</sub>O<sub>2</sub>. Second, the addition of <sup>1</sup>O<sub>2</sub> to iodide anion forms peroxyiodide that decomposes to give H<sub>2</sub>O<sub>2</sub> and iodine. The potentiation of the PACT effect was also demonstrated by treating the *in vivo* oral *Candida* infection model in an immunosuppressed mouse. The disease was cured in 5 days with a combination of methylene blue and KI [42]. The ROS was also higher in a BSA-carbon dot (BSA-CD) conjugate prepared through carbodiimide chemistry, where the increased ROS production was attributed to the high triplet yield [43]. This probability was evident from the reduced fluorescence lifetime of BSA-CD (9.08 ns) compared to CD (11.27 ns) under the 525 nm excitation [43].

The excitation sources also influence the PS activation and <sup>1</sup>O<sub>2</sub> production [44]. Both coherent (lasers) and non-coherent (halogen lamps and LEDs) light sources have been used to excite PSs [45]. An updated list of experiments using different light sources is given in Table 1. Soria-Lozano *et. al.* [46], concluded that the efficiency would be more if the wavelength was tuned to the PS excitation

window. In this regard, lasers are promising excitation sources as the lights possess monochromaticity and coherence. Laser diodes have been tested in the recent past as excitation sources for PACT with an excellent killing efficiency. Compared to laser diodes, LEDs are cost-effective in optimizing the PACT protocol. Similar to lasers, LEDs also emit monochromatic radiation but are incoherent. LEDs can be placed between conventional lamps and lasers in terms of spectral properties, cost, and light emission features [47, 48]. Very low heat emission by LEDs than incandescent bulbs release 90% of their energy as heat and are attractive to PACT. A 20 minutes irradiance of methylene blue has been shown to kill more than 93% of the bacteria [49]. Recent studies also used LEDs with naturally occurring PSs like curcumin to kill a range of Gram-negative and -positive pathogens [50-52]. Additionally, studies have also shown that the NIR lasers (980 nm) rapidly heal localized deep tissue infections of Methicillin-resistant *Staphylococcus aureus* (MRSA) in mice [53]. However, this efficacy was reduced significantly by increasing the tissue thickness from 5 mm to 10 mm [53]. Recent studies proposed organic LEDs (OLEDs) for transforming PDT of skin infections and cancers through homecare treatment practice [54]. For example, parallel-stalked flexible OLEDs suitable for various low voltage, high power wearable optoelectronic applications have been designed recently, which could improve  $^1\text{O}_2$  production by a factor of 3.8 compared to a reference OLED [55]. A few examples of OLED-based PDT and PACT are highlighted in Table 1.

**Table 1:** List of light sources, excitation, wavelengths, PSs, and applications of PACT.

Light Source	$\lambda_{\text{ex}}$ (nm)	PS	Application/target	Ref.
Halogen lamp		Methylene blue (MB)	Food-borne pathogen	[56]
	560-780	Toluidine blue O (TBO)	Clinical practice	[57]
		Erythrosine	Dental medicine	[58]
	450-500	Eosin-Y, Rose Bengal, Curcumin	Dental medicine	[59]
	350-500	Tris-(4,7-diphenyl-1,10-phenanthroline)ruthenium (II) dication (RD3)	Dental medicine	[60]
	600-700	RLP068/Cl (Zn(II) phthalocyanine chloride)	Clinical application	[61]
	>500	PEGylated purpurin 18 derivatives	Cancer treatment	[62]
Laser	660	MB	Dental medicine	[63]
		Malachite green		
	635	TBO	Dental medicine	[52]
	810	Indocyanine green		
	635	Pthalocyanine (ZnPcOPyMe)	Multidrug-resistant bacterium	[64]
	684/685	MB	Antifungal treatment	[65]
665	MB	Dental medicine	[66]	

	660	MB	Veterinary medicine	[67]
	635	Methyl aminolevulinate	Dermatology	[68]
	630	Porfimer sodium (Photofrin)	Veterinary medicine	[69]
	650	pyropheophorbide-a derivatives	Cancer treatment	[70]
LED	450	Curcumin	Dental medicine	[52]
	470	Curcumin	Foodborne/food spoilage bacteria	[48]
	470	20-(4 carboxyphenyl)-2,13 dimethyl-3,12-diethyl-(22 $\pi$ ) pentaphyrin (PCCox)	Water disinfection	[71]
	663	MB	Inhibition of bacteria, yeast, and microcrustacean growth	[49]
	465	Tetra-cationic 5,10,15,20-tetrakis (1-methyl-4-pyridinio) porphyrin tetra (p-toluenesulfonate) [TMPyP]	Inactivation of aquaculture pathogen	[72]
	465	Cationic porphyrin TMPyP	Sterilization of Microalgae	[73]
	633	5-Aminolevulinic acid (ALA)	Dermatology	[74]
	650	BDPY nanoparticles	Ophthalmologic treatment	[75]
	640 $\pm$ 5	MB+TBO	Dental medicine	[76]
	420-480	Curcumin	Dental pathogens	[77]
	630	Photogem® (a porphyrin)	Disinfection of Blood	[78]
	450	Curcumin	Food pathogens	[79]
	430 $\pm$ 10	Curcumin derivatives	Cancer treatment	[80]
OLED	671 $\pm$ 140	MB	Leishmaniasis	[54]
	626	5-aminolevulinic acid	Cancer treatment	[81]
	660	BODIPY	Cancer treatment	[55]
	669 – 737	MB	Antibacterial	[82]
	550-750	Aminolaevulinic acid	Cancer treatment	[83]

### PS-bacteria interaction in PACT

Photosensitizers are natural (mostly aromatic molecules) or synthetic compounds that can participate in an energy/electron transfer reaction and sensitize the nearby molecular oxygen to generate  $^1\text{O}_2$  or ROS, killing microorganisms in the proximity [21]. An ideal PS is expected to have a prominent absorption in the 650-850 nm wavelength region to have high tissue penetration and sufficient triplet state energy for  $^1\text{O}_2$  generation [84]. Amphiphilic PSs are ideal for PACT because they show higher solubility in the water while maintaining their ability to diffuse across the hydrophobic cell membrane and accumulate inside the bacteria to enhance the phototoxic activity [85]. More importantly, such molecules should be nontoxic in the absence of light [21]. Intracellular distribution and organelle-

specific localization of a PS depend on its hydrophobicity, the type and number of charges, the charge to mass ratio, and the chemical structure [86].

PSs are classified based on their origin, chemical composition, and interaction mode [21, 87, 88]. In PDT, PSs are classified into first generation, second generation, and third generation. In addition, new generation metal and semiconductor nanoparticles have been recently applied, which can be grouped into the fourth generation PS nano drugs for PDT and PACT. These PSs are classified in recent review articles [89-92]. There are three types of antimicrobial PSs: those, which can tightly bind and penetrate microorganisms, those loosely bind, and those that do not bind at all. Poly -L-lysine chlorine (e6), (pL-ce6) conjugate is an example of the first type, which attaches well to pathogens' negatively charged cell wall and penetrates Gram-negative bacteria. Demidova *et. al.* [93] showed that the pL-ce6 conjugate is more effective towards *E. coli* than *S. aureus*. This effectiveness is explained by the large molecular weight of the conjugate, which reduces its ability to penetrate Gram-positive bacteria's outer peptidoglycan. In Gram-negative bacteria, the conjugate penetrates the outer membrane by the process of "self-promoted uptake." The conjugate's positive charges replace the divalent cations in the LPS, distort the outer membrane structure, and allow channel formation. Toluidine blue O (TBO) is a phenothiazinium class of dyes, which was more effective when remaining in the suspension than internalized [88]. This efficiency may be due to two reasons: 1) light-mediated extracellular generation of the ROS that diffuses into the cell, 2) an initial PACT action produces some damage at the cell surface, allowing more TBO molecules present in the solution to bind or penetrate the cell. Rose Bengal, a xanthene class fluorescent dye, enters the cell through a diffusion-controlled process rather than active binding to the cell [88, 93].

Early reports on PACT used first-generation PSs such as methylene blue, Rose Bengal, and toluidine blue, and they are efficient even against antibiotic-resistant strains [94]. Methylene blue, a commonly used dye in microbiology, has an absorption maximum between 600-670 nm, and at higher concentrations, they showed antibacterial and antifungal properties even in the absence of light [95]. When used as a PS at a low concentration, they efficiently killed Gram-negative and -positive bacteria and fungi [49]. Another widely used PS, Rose Bengal (RB), is a xanthene-based bright bluish pink dye with optical absorption in the 450–650 nm region. Several studies supported the use of RB as a PS to kill the planktonic and biofilm-forming *Enterococcus faecalis*, *Streptococcus* sp., and *Vibrio* sp. [22, 46, 59]. In a PACT reaction, the ROS produced by RB kills bacteria by interfering with the cell wall integrity, metabolism, and DNA stability [22]. TBO, another phenothiazinium dye, was also reported

to kill bacteria by causing membrane damage [96]. The use of TBO in combination with light is reported to be efficient in killing more than 85% of *E. faecalis* [52], *V. vulnificus* [97], and *S. mutans* [98]. Further, antibacterial studies showed no toxic effect of TBO when applied without the light.

Porphyrins and their synthetic derivatives are second-generation PSs. They are water-soluble biochromes, including the hemoproteins like chlorophyll, hemoglobin, cytochromes, catalases, etc., that can be excited between 600-690 nm range [99]. The maximum light absorption in the visible region, rapid triplet state formation, high quantum yield, and versatile structural properties make them ideal candidates for PACT [6]. There are different derivatives of porphyrins available in the market. A meso substituted cationic porphyrin (Tri-Py<sup>+</sup>-Me-PF) exhibits phototoxicity against both Gram-positive and -negative bacteria under low light dosages [100]. The conjugates of neutral or anionic porphyrins with cationic antimicrobial or cell-penetrating peptides like apidaecin show more vital interaction with bacterial cell walls and enhanced phototoxicity on exposure to the light [101].

Phthalocyanines are another class of PSs with a backbone of isoindole subunits linked together by secondary amine bridges. The excitation range of phthalocyanines lies between 660-700 nm. The Zn derivatives of phthalocyanines (ZnPc) have been reported to kill the Gram-positive pathogen, *Streptococcus mitis*, by impinging the membrane protein stability [102]. The electrostatic repulsion of phthalocyanines by Gram-negative bacteria's cell wall makes them less preferred PSs for the latter group of bacteria like *Escherichia coli* [103]. However, this repulsion can be reversed by conjugating with cell-penetrating peptides or other cell membrane damaging compounds like EDTA [61, 104, 105].

Recent studies also showed natural extracts of Riboflavin, Hypercins, and Curcumins as potential PSs in PACT. Riboflavin is among the essential vitamin B complex group. It is a yellow-green fluorescent and water-soluble pigment with maximum optical absorption between 220 – 450 nm [106]. Upon excitation, riboflavin induces reactive oxygen stress leading to respiratory chain impairment and cell wall damage in bacteria [107]. The PACT using Riboflavin as the PS efficiently inhibits keratitis-causing microorganisms [108] and kills clinical isolates of *E. coli* [107], *E. faecalis* [109], methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* [24]. The need for excitation wavelength in the 220-450 nm range is a significant limitation of riboflavin since such high-energy photons induce reactive oxygen stress and mutations. Differentiating the phototoxicity generated through the direct effect of light or a PS is difficult. Recently, Maisch *et. al.* [24] synthesized a derivative of riboflavin with excitation in the 380–600 nm range and ~75 % <sup>1</sup>O<sub>2</sub> quantum yield. The molecule's additional positive charge enables it to attach to the negatively charged

surface of Gram-negative pathogens, facilitating the fast and efficient antimicrobial activity. Hypericin, another natural PS based on anthraquinone extracted from Saint John's wort (*Hypericum*), has an absorption maximum of 593 nm [110]. Photosensitization of hypericin using high-power pulsed light has been proposed as a strategy to kill the food pathogens, which suppresses the Gram-positive *Listeria* sp. and the Gram-negative *Salmonella* sp. [111]. Aggregation-induced emission luminogens (AIEgen) differentiated Gram-negative and -positive bacteria and showed efficient antibacterial activity against Gram-positive bacteria on photoexcitation with different light sources [16, 112].

Curcumins, optically active compounds found in the root tuber of Turmeric (*Curcuma longa*), are relatively new PS in PACT. Curcumins are yellow-colored polyphenolic pigments with 420-460 nm excitation wavelength and are sparingly soluble in water. The crude extracts of curcumins were used in ethnic pharmacology for anti-inflammatory, antioxidant, antibacterial, and hypoglycemic activities [113, 114]. Ayurvedic medicine in India historically proposed the use of a crude extract of curcumin for topical applications. Later proved scientifically, the application of curcumin against bacterial infections in wounds exposed to as an example of PACT. Several studies have shown that the photoexcitation of curcumin could reduce the growth of *Enterococcus faecalis*, *E. coli*, and *S. aureus* [50-52, 59]. However, certain studies indicated that curcumins as PSs are less efficient towards *S. mutans*, *S. sanguis* and *C. albicans* than many other common PSs like Rose Bengal or Methylene blue [46]. Hence, further studies are required to differentiate between curcumins' inherent and photoinduced antibacterial properties and define the combinations of excitation source and concentration of curcumins. Coumarin-based PSs with NIR emission and large Stokes-shifts were synthesized recently, which bind with the plasma membrane and kill the animal and bacterial cells through ROS formed by white light exposure [115]. Apart from the chemically characterized curcumin derivatives, crude extracts of curcumin-producing plants were also tested as PSs. The use of plant extracts or natural compounds as PSs in PDT of cancer has been reviewed recently by Mansoori *et. al.* [5]. However, the application of crude extracts in PACT is unexplored.

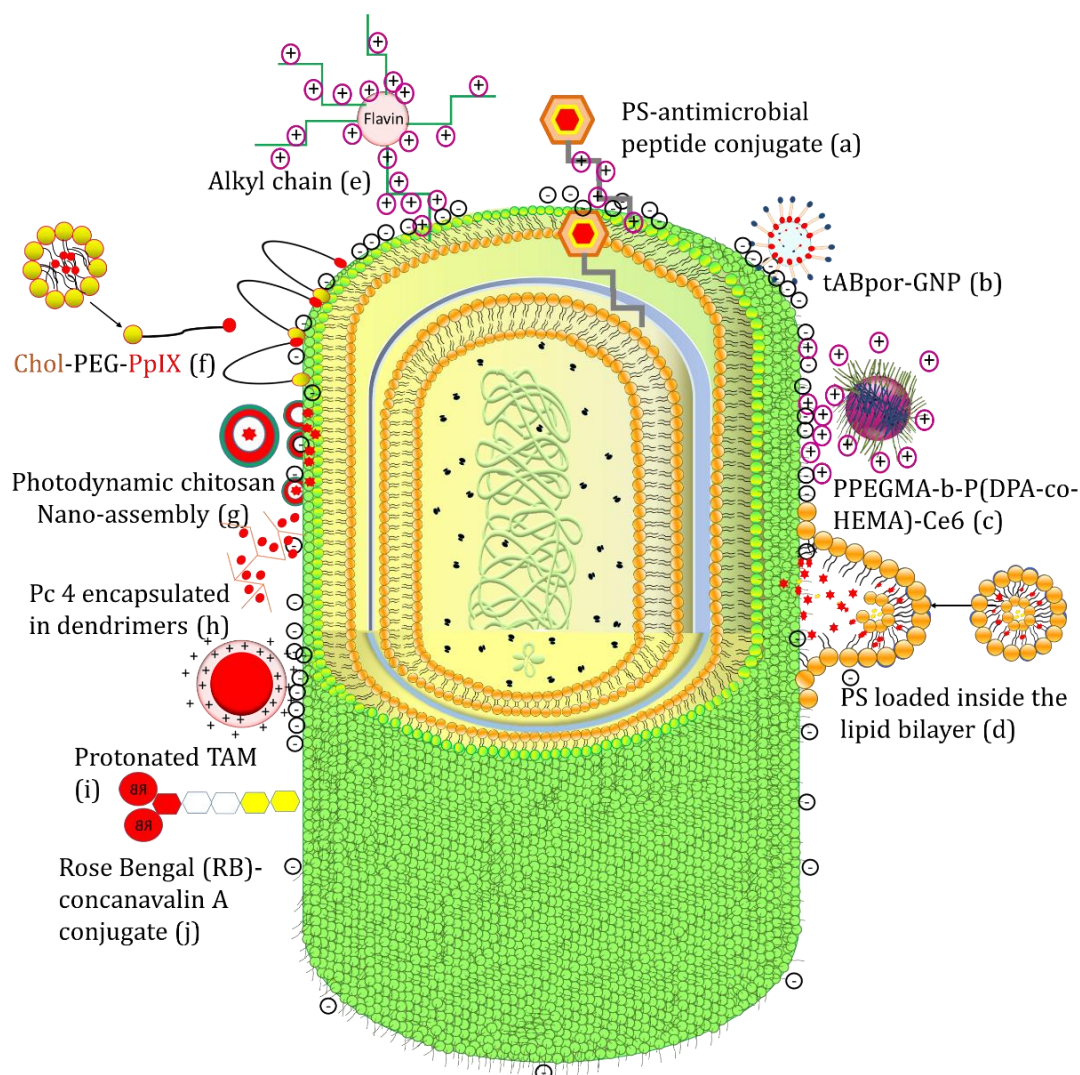
Engineered nanoparticles are the recent addition to the library of PSs [7], and the major ones include quantum dots [116, 117], carbon nanotubes [113, 114], fullerenes [113, 115], graphenes [118-120], conjugated polyelectrolytes [121], gold nanoparticle [122], TiO<sub>2</sub>, and ZnO [123]. Photoactivated fullerene derivatives were found to kill bacterial and fungal pathogens through ROS-mediated membrane destabilization and DNA damage [120]. Reports show that CdSe/ZnS QDs produce <sup>1</sup>O<sub>2</sub> [120, 124-127] and induce damage or breakage to plasmid DNA in proximity through ROS production

on photoexcitation [116]. But this ROS-mediated toxicity of CdSe/ZnS QDs was not visible when it was conjugated with whole cells of *Vibrio* sp., where the bacterial cell wall and DNA remained intact [127]. This QD's internalization through the cell membrane of bacteria was ruled out as the hydrodynamic size of the QD was larger than the largest globular protein that can pass through the intact bacterial membrane. Similar results were observed when the graphene QDs (GQDs) alone were applied to bacterial and animal cells, while a combination of GQDs with methylene blue induced photodynamic killing [128, 129].

Interestingly, the nitrogen-doped GQDs produce more ROS than those lacking the nitrogen, and the luminescence of these particles supported the simultaneous tracking and killing of bacteria [129]. A mesoporous silica nanoparticle embedded with carbon nanoparticles and RB was reported for a similar purpose of tracking the position of drugs and PDT [130]. A PS nanomaterial with promising antibacterial activity against *E. coli* and MRSA was fabricated recently by incorporating tetra-(4-carboxy phenoxy) phthalocyanine zinc PS through amidation reaction to the metal-organic framework UiO-66-NH<sub>2</sub> [131]. Similarly, a chlorin e6 containing nanoparticle prepared *via* the carboxyl-amine reaction or the acyl chloride-amine reaction with cholesterol and polyethyleneimine could interact with the bacterial cell wall through electrostatic interactions and eradicate Gram-positive and Gram-negative bacteria [132].

Although there are no reports on developing resistance against a photodynamic reaction, concerns about ROS's nonspecific interactions with the host cell must be accommodated. This problem has been addressed in different ways. For example, some studies attempted to use engineered PSs specific to pathogens [133], whereas some reported that the photosensitization reactions are not toxic [134]. Several strategies have been proposed to enhance the efficiency of PACT through the site-specific delivery of PSs, which along with the short lifetime and narrow diffusion range of PSs reduce their toxic effects (Figure 3). The strategies are broadly focused on targeting the bacterial cell surface for internalizing PSs. Targeting the cell surface is achieved by surface modifications, encapsulation, or conjugation of PSs with other molecules to improve the charge-based interaction with the bacterial cell wall. The outer surface of the bacterial membrane has a significant negative charge compared to the animal cells, promoting the electrostatic interaction with positively charged PSs [3]. Triarylmethane dyes (TAM) with protonatable groups interact selectively with the bacterial cells compared to animal cells, facilitating the selective photokilling of pathogens [3]. In another study, Maisch *et al.* added

multiple positive charges to flavin derivative using a short alkyl chain linker to enhance its binding with the negatively charged bacterial cell wall [24]. A pH-sensitive PS conjugate,



**Figure 3.** A scheme of different strategies to enhance the interaction of PSs with bacterial cells and enhance the PACT efficacy. This scheme is a compilation of the finding in the reports given in brackets next to each mode of interaction: a) [135], b) [136], c) [137], d) [138], e) [24], f) [139], g) [140], h) [141], i) [3], j) [20] .

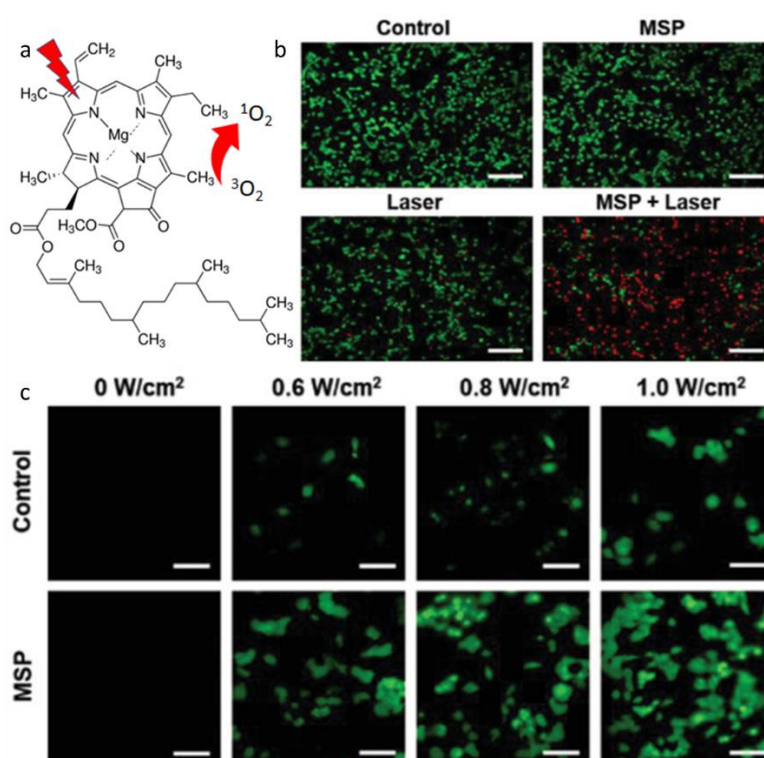
poly(polyethylene glycol) methyl ether methacrylate)-*b*-poly(diisopropylamino) ethyl methacrylate-*co*-2-hydroxyethyl methacrylate)-chlorine6 (PPEGMA-*b*-P(DPA—*co*-HEMA)-Ce6), synthesized by reversible addition-fragmentation chain transfer (RAFT) was found to increase the positive charge from -1.45 to +11.6 mV with the change in pH from 7.4 to 6.0. This property is applied to photokilling *E. coli* and *Staphylococcus aureus* [137]. In a recent study, Jia *et al.* [139] proposed a cholesterol-



assisted bacterial cell surface engineering strategy, in which the protoporphyrin IX (PpIX), polyethylene glycol (PEG), and cholesterol were conjugated to form micelle-like nanoparticles in an aqueous solution. The micelle releases PpIX on encountering bacteria, and cholesterol supports its binding with the cell wall to localize ROS action. Rose Bengal conjugated with a lectin, concanavalin A (ConA), also facilitates the targeting of Gram-negative bacteria, utilizing the ability of ConA to bind specifically to the mannosyl and glucosyl residues of the lipopolysaccharide layer [20].

The encapsulation of PSs in liposomes, semi-solid formulations, and nanoparticles has also been found effective in site-specific release and enhancing PACT efficiency [136, 138, 142]. Cationic liposomes are effective in targeting a PS to the bacterial cell through electrostatic interactions [138]. The PS (trans-AB-porphyrin) incorporated in a gelatin nanomatrix (< 200 nm) was found to effectively kill both Gram-negative and -positive bacteria [136]. The nano-assembly of the PS chlorin e6 with chitosan nanoparticle effectively targets the bacterial cell wall of Gram-positive and -negative bacteria, showing the photodynamic antibacterial property [140]. Intracellular delivery of PSs is another promising strategy that has been experimented with successfully to enhance the photokilling of bacteria. This killing was achieved in the presence of divalent cations by conjugating the PS with cell-penetrating peptides, dendrimers, or efflux pump blockers [135, 141]. The medium influenced the self-promoted uptake of PSs like Rose Bengal and Methylene blue by certain bacteria by divalent cations like Ca and Mg [143]. The concept of using cell penetrating peptides for intracellular delivery of a PS was evaluated initially by Johnson *et al.* who demonstrated that the eosin Y conjugated with antimicrobial peptide (KLAKLAK)<sub>2</sub> can inactivate 99.999% of 10<sup>8</sup> colony forming units (CFU) mL<sup>-1</sup> of bacteria [135]. A hydrogel preparation that could induce photothermal and photodynamic effects, as reported recently, where the former increases the permeability of bacterial cell walls by increasing the temperature. Simultaneously, the ROS generated in the latter easily access the intracellular environment through these pores and exhibited severe antibacterial activity [144]. A novel BisSe<sub>3</sub> nanoparticle coated with polyethyleneimine (PEI) also showed similar properties and killed approximately 99% of *S. aureus* and 97% of *E. coli* within 10 minutes of irradiation using a NIR laser (808 nm) [145]. The contribution of photothermal and photodynamic effects in the bacterial killing was found 4:1. The upregulation of heat shock proteins and resultant 2 log<sub>10</sub> less killing among *E. coli* exposed to the pre-treatment with heat than PDT with TBO alone are valuable for combination therapies [146].

In an interesting study, a biohybrid was prepared by decorating the *E. coli* cells with a nanoparticle PS for imaging and PDT of cancer cells [147]. Another recent finding was designing photosynthetic biohybrid nano-swimmers composed of a magnetic engineered bacterium- *Spirulina platensis*, targeting tumor cells using a magnetic force. The chlorophyll contents are released, degrading the bacterial cell wall with the help of X-ray radiation [148]. The chlorophyll supplies oxygen to tumor cells, otherwise hypoxic at a low pH, and shows vascular abnormalities and resistance to many drugs. The internalized chlorophyll molecules initiate ROS production in more than 70% of mouse 4T1 breast cancer cells, which could kill  $66 \pm 3.8\%$  of 4T1 cells [148] (Figure 4). Further, an 82 % reduction in the tumor volume compared to the initial volume



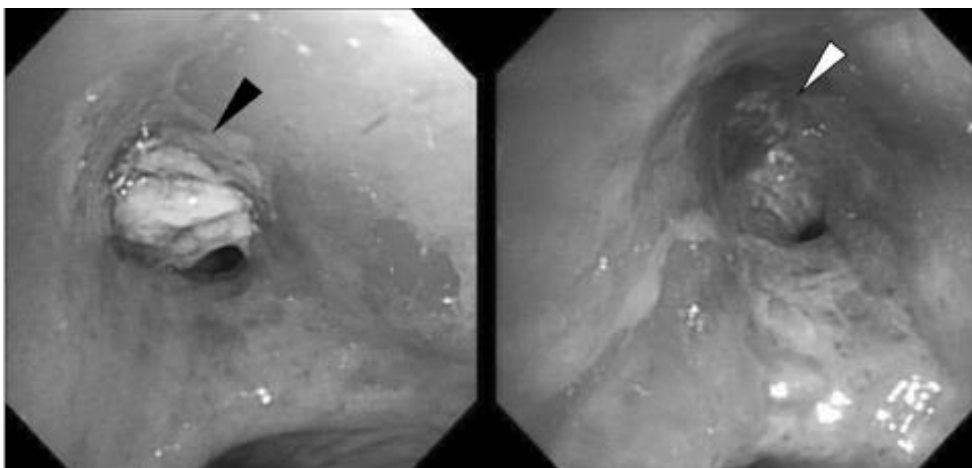
**Figure 4.** *In vitro* evaluation of magnetic *S. platensis* based hypoxia regulation and photodynamic therapy. a) The process of  $^1O_2$  production by chlorophyll a. b) Representative microscopy images of 4T1 stained with Calcein-AM (green, live cells) and PI (red, dead cells) after different treatments. Scale Bar = 200  $\mu\text{m}$  (taken from [148]). (c) Representative fluorescence images of 4T1 cells stained with ROS stain DCFH-DA after a 650 nm laser irradiation (0-1  $\text{Wcm}^{-2}$ , for 10 min) with/ without preirradiated MSP. Scale Bar = 100  $\mu\text{m}$ . 'b' and 'c' are taken from ref. [148]

of  $\sim 50 \text{ mm}^3$  was recorded when the tumors were injected with 100  $\mu\text{L}$  of magnetic *S. platensis* ( $200 \mu\text{gml}^{-1}$ ) and exposed to a combination of X-ray (6 Gy) followed by 650 nm laser ( $1 \text{ W cm}^{-2}$  for 600 s) [148]. In a similar strategy, tumor-targeting conjugates of *Synechococcus* strain decorated with indocyanine green encapsulated human serum albumin nanoparticles were found to enhance tumor

cells' oxygen concentration by photosynthesis of *Synechococcus* on exposure to the 600 nm laser [149]. The released oxygen increased the photodynamic effect of indocyanine green on exposure to the 808 nm laser [149]. Another report used a combination of photosynthetic cyanobacteria, *Synechococcus*, and chlorin e6 for tumor oxygenation, followed by the photodynamic killing of tumor cells [15]. A self-propelling PS conjugate was designed to improve PDT efficacy by improving tumor cell oxygen concentration [150]. The design includes a self-propelled magnetic nanoparticle attached to a porphyrin PS. This motor's active movement is by ionic diffusiophoresis, induced by enzymatic decomposition of urea, which significantly enlarges the coverage area of the nanoparticle-conjugate by ten times to spread ROS inside the cell, thus enhances the PDT efficacy [150].

### Applications of PACT

PDT has been widely experimented with curing several types of cancers since the first report from Mayo Clinic ca 1960 by Lipson and Schwarts [5, 10, 12, 14, 69, 117, 118, 151-154]. Remarkable achievements were observed in the photodynamic treatment of non-melanoma skin malignancies [155], low invasive bladder cancer [156], and non-small-cell lung carcinoma (NSCLC) [157]. One successful demonstration was the clinical trial to cure NSCLC using intravenously administered Radachlorin® solution followed by laser irradiation using the flexible fiber-optic bronchoscopy [157]. The bronchoscopic images of the 79-year-old patient (Figure 5) adapted from the work of Ji *et al.* (2013) showed the left upper lobe of the bronchial lumen, which was recanalized



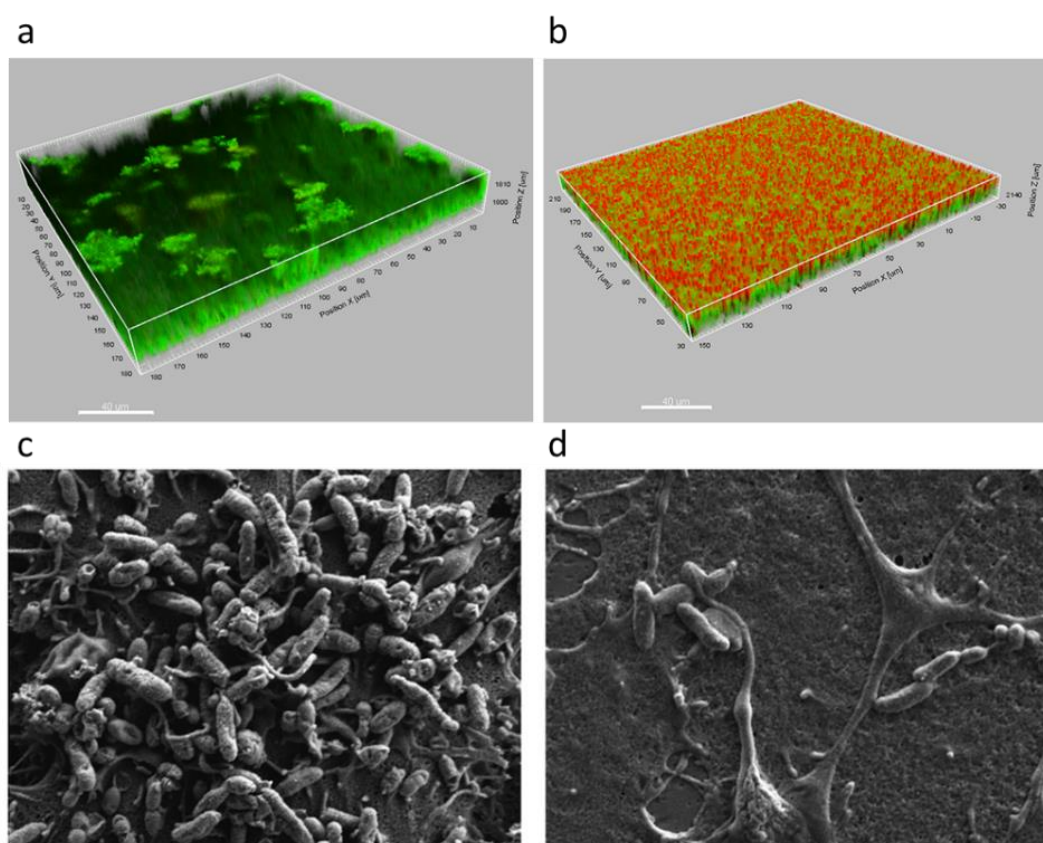
**Figure 5.** Bronchoscopic image of a 79-year-old patient whose bronchogenic carcinoma with central airway obstruction in the left upper lobar bronchus (black arrowhead) was effectively recanalized (white arrowhead) using PDT, reproduced with permission from ref.[157].

successfully with PDT. Further developments in the clinical status of PDT in cancer treatment are found in several review articles [158-161]. Although similar studies have been conducted to explore PDT in killing microorganisms, the recent advancements in the area are less reviewed. PACT has successfully experimented in the control of skin and periodontal infections in animals [59, 162-169], removal of foodborne pathogens [170, 171], inactivation of multidrug-resistant pathogens in the wastewater [172], killing pathogens of veterinary and aquatic animals [22, 67, 173, 174] or self-disinfecting textiles and polymers [175, 176].

PACT is proven to be more effective and focused on controlling dental infections and implantology, with added advantages of reducing the emergence of antimicrobial resistance and patients' allergy to certain antibiotics [177-180]. PACT was demonstrated as an adjunctive treatment modality with nonsurgical treatment, such as scaling for chronic periodontitis and mechanical debridement [181-183]. The adjuvant effect of PACT remains debatable, with certain reports showing it ineffective in removing the bacterial load in challenging clinical situations such as smokers [184, 185]. It may be possible to overcome these difficulties by selecting appropriate PSs and optimizing their concentrations, exposure time, light sources, and chemical variables (pH, exudates, and gingival fluid) of the treatment area [184]. PACT is the second-best for He/O<sub>2</sub> cold jet plasma treatment in disinfecting root canals [186]. Besides conventional therapy, PACT offers improved microbial disinfection, leading to a successful long-term outcome [187]. *In vitro* studies indicate that PDT had achieved 90.1 to 98.8 % bacterial killing efficiency, which was comparable with triple antibiotic paste (99.9 %) and the recently introduced GetleFile irrigation activation system (99.8 %) in root canal disinfection [188, 189]. Although many studies advocate the potentials of PACT in dental treatments, the efficacy of microbial killing varies between cases, depending on the PS concentration and the laser intensity [46, 190]. This could also be due to different interactions of PSs with various bacteria and inhibition of the bacterial uptake of PSs by the serum components and quenching of ROS by tissue fluids [191, 192]. Therefore, PACT studies need further attention to identify novel PSs, light sources, optimized PS dosages, exposure time, and other treatment parameters to obtain consistent results.

Skin infections and biofilm formation by multiple antibiotic-resistant pathogens like *Pseudomonas* sp., *Streptococcus* sp., *Staphylococcus* sp. *Moraxella* sp., and *Candida* sp. were controlled with PACT [193]. The biofilm-forming bacteria are complicated to be killed using antibiotic therapies as the complex biofilm functions as a barrier to reduce the effective concentration of antibiotics inside the matrix. Microbial infections of the skin and mucosa can be easily treated using

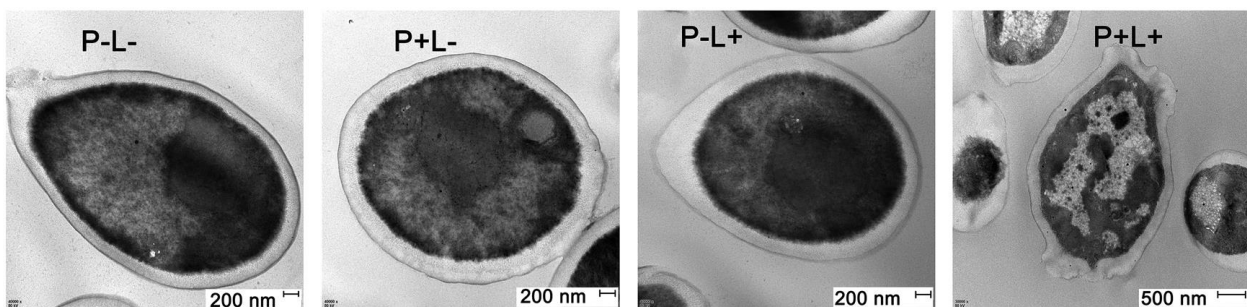
PACT by exposure to a PS and a light source. The polymeric matrix covering the bacteria is known to slow down the diffusion of antibiotics and thus functions as the first defense line for the cells living inside the biofilm [194]. However, the polysaccharides, proteins, and lipids in the biofilm are amenable to oxidative stress under PDT [193]. A deoxyribonuclease decorated gold nanoparticle was found to destabilize 80% of the biofilm and kill 90% of bacteria under the photoexcitation using an 808 nm laser [122]. A significant reduction in the abundance and morphological structure of biofilms formed by *Moraxella catarrhalis*, *S. aureus*, *S. pneumoniae*, and *P. aeruginosa* are reported [195-198] (Figure 6). The disruption of biofilm integrity would also improve the diffusion and efficacy of antibiotics [198, 199]. PDT with 5-aminolevulinic acid was found to detach the biofilm of *S. haemolyticus*, and the subsequent gentamicin treatment killed the bacterial cells [200].



**Figure 6.** Representative (a, b) laser scanning confocal microscopy (scale bar: 40 µm) and (c, d) scanning electron microscopy images (x 5000 magnification) of biofilms before (a, c) and after (b, d) PACT. Reproduced with permission from ref. [198] (a, b) and ref. [197] (c, d).

The killing of fungal pathogens on the skin is tricky as the chemicals used to kill this eukaryotic organism can also be toxic to the host cells. This difficulty can be minimized with PACT because the oxidative stress tolerance mechanisms of humans and animals are much advanced compared to

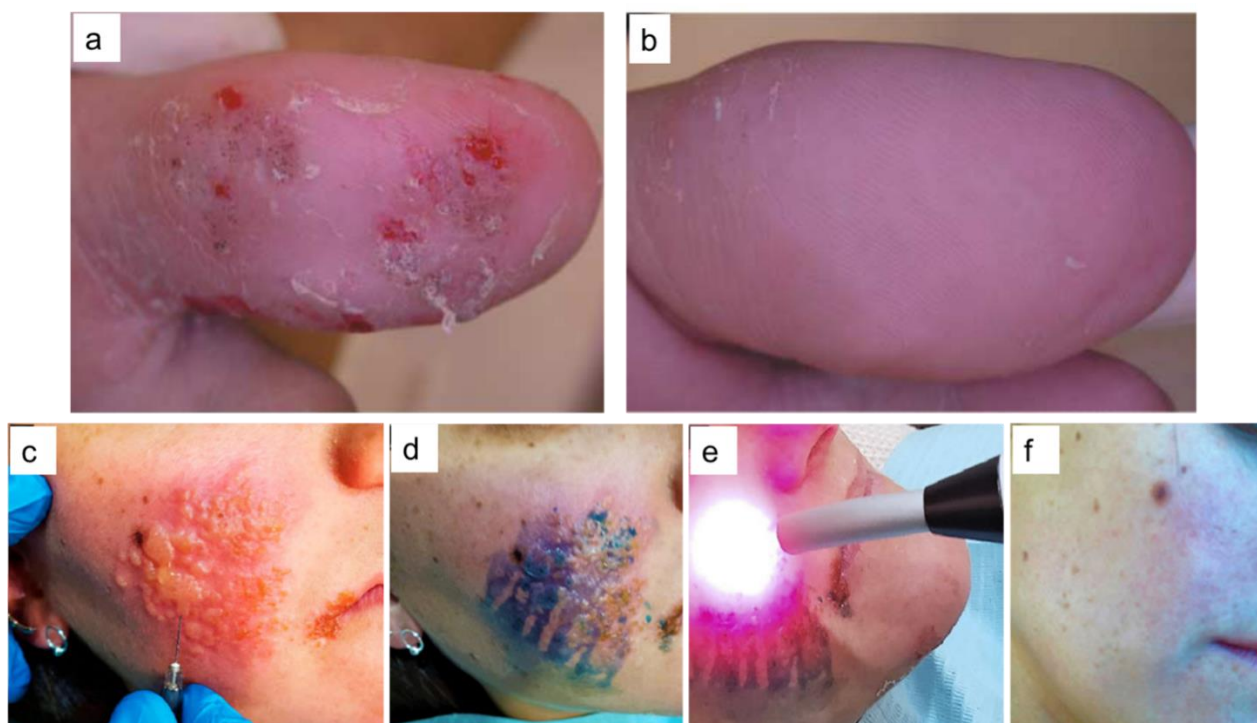
microbial pathogens [201, 202]. Application of hydrogels containing a PS and exposure to a LED light beam for 14 min was found to reduce *C. albicans* infections in the tongue of 6-week old Swiss mice [203]. Exposure of localized candidiasis infection to methylene blue and a laser (660 nm) for less than a minute was found more effective than the fluconazole (100 mg day) treatment for 14 days [204]. The recurrence of the infection was not found in the former case for more than 30 days, while the latter could not prevent even a (one week) short-term recurrence. The *in vitro* studies with aloe-emodin, a PS extracted from Aloe vera, were found to induce damage to the cell wall, cytoplasm, and nucleus of *C. albicans* [205]. This effect was evident from the transmission electron micrographs of the clinical isolates of azole-resistant *C. albicans* (Figure 7).



**Figure 7.** TEM image of azole-resistant *C. albicans* clinical isolates before (-) and after (+) treatment with 100  $\mu$ M PS (P) at 37  $^{\circ}$ C for 30 min and irradiated (L) with 96 J  $\text{cm}^{-2}$  white light (400-780 nm) for 20 min. Reproduced with permission from ref. [205].

PACT has a significant advantage over other therapies for viral infections, such as curing the localized lesions of herpes and warts and sterilizing blood [206-211]. An eight-month-old study in twelve patients showed that warts could be entirely cured using 5-aminolevulinic acid (ALA) as the PS (Figure 8 a, b)[212]. Similarly, in a recent clinical trial, the Herpes zoster virus infection was cured on a young patient's skin (Figure 8c -f) [213]. Viruses are more amenable to ROS owing to their simple structure. ROS can abstract hydrogen from proteins, induce peroxidation of lipids, and damage genetic materials, leading to the structural disintegration of viral proteins and inactivation of enzymes. The developments of PACT in the last 25 years in controlling respiratory tract infections by bacterial, fungal, and viral pathogens are recently highlighted. Also, the possibility of PACT for fighting COVID-19 is discussed recently [208]. The possible role of the PS, methylene blue, in the treatment of COVID-19 was proposed by Ghahestani *et al.* [214], based on the absence of viral infections in a cohort of 2500 cancer patients treated with methylene blue [215]. Since the lower respiratory systems are one of the critical infection areas of SARS-CoV-2 and are relatively easy to irradiate using an

optical fiber, the application of PACT to COVID-19 patients is a promising strategy [216]. A recent study reported the inactivation of SARS-CoV-2 in the blood using methylene blue [217]. PACT can also be used to sterilize blood and blood components, which otherwise may lead to severe disease conditions like HIV and hepatitis in recipients [78]. However, the limited availability of PSs compatible for application to blood samples is a limitation [218].



**Figure 8.** Images showing the clinical efficiency of PACT in curing warts [17] and herpes [213] infection. a) Viral wart over the planar surface of the left big toe of the patient; b) Complete disappearance of the wart after four applications of PACT. c) Herpes virus infection on the cheek after breaking the vesicles using a needle. d) Application of 0.002% methylene blue over the affected area. e) Light irradiation using a red LED (660 nm, 18 J). f) Completely cured wart without evidence of recurrence after eight-month observation. Reproduced with permission from ref. [212] and [213].

The combinations of PSs and fibroblast growth factors are promising strategies with the dual function of infection prevention and skin growth in severely burned patients [163, 219]. An efficient hydrogel for this dual function can be prepared from carboxymethyl chitosan (CMCS)-sodium alginate, embedded with nanospheres composed of sinoporphyrin sodium (DSDMS) and poly(lactic-co-glycolic acid) (PLGA)-encapsulated basic fibroblast growth factor (bFGF). This hydrogel eradicated almost 99.99% of *S. aureus* [163]. Statistical tools such as Box-Behnken design for response surface methodology help design a hydrogel and the PS release rate. Such a design efficiently

eradicated MRSA [220]. Further optimization of these developments included using a smartphone-based fluorescence detection to guide the uniform application of PSs on the area of infection and avoid the nonspecific interactions [221]. Animal studies were also conducted to demonstrate the efficacy of PACT in curing psoriasis [222, 223].

PACT can also be used as a preventive strategy for disinfecting near-patient surfaces and devices to control the spread of nosocomial pathogens. Laboratory and hospital studies indicated that a surface with a photodynamic coating could significantly reduce the bacterial load below the benchmark of 2.5 CFU cm<sup>-2</sup>. The efficacy was retained for an extended period [224]. Similar strategies have also been reported for preparing self-adhesive bandages and photodynamic polymers [176]. The elastomer containing photoactive antimicrobial [ $\sim 1$  wt % zinc-tetra (4-N-methylpyridyl) porphine (ZnTMPyP<sup>4+</sup>)] prepared by Peddinti *et al.* [176] effectively disinfected more than 99% of bacterial and viral particles within 30 min. A polyurethane sample impregnated with crystal violet and 3 – 4 nm size zinc oxide nanoparticles was found effective in killing a significant fraction of nosocomial pathogens (*Pseudomonas aeruginosa*, MRSA, and *E. coli*) and even endospores of *Clostridium difficile* under laboratory conditions [225]. Recent studies have also reported the potentials of PDT in the preparation of self-sanitizing textiles, which could achieve a 98% reduction in the viability of bacterial cells by 30 min photoactivation [175]. The AIE-active benzothiadiazole and tetraphenylethylene (TPE) conjugate polymer (PTB-APFB) prepared by Zhou *et al.* (2020) by introducing a donor-pi-acceptor (D- $\pi$ -A) structure to the skeleton incorporating azidoperfluorobenzoate (APFB) moiety in the side chain was found to generate significantly high levels (>11 times) of ROS compared to chlorine-e6. The PTB-APFB was efficient in killing the pathogenic bacteria *S. aureus* and *E. coli* and the fungus *C. albicans* in a solution or associated with a skin infection in a mouse model [226].

Replacing the application of antibiotics and other chemicals in the food processing, sewage/ water treatment, veterinary and aquaculture sectors are equally important as they can ultimately pose a threat to humans. Photodynamic disinfection is safer than UV treatment for food materials and has been experimented with to decontaminate cheese, meat, and fruits [48, 56, 170, 171, 227]. The leakage of pathogens from sewage treatment systems to the natural ecosystems is a significant problem, which can cause the community to spread diseases like cholera. There is little concern about microbial disinfection in sewage treatment systems, and the wastewater released into rivers and estuaries after secondary treatment may have a high load of microorganisms. Photodynamic disinfection has the dual advantage of killing pathogenic microorganisms and degrading organic pollutants in sewage treatment



systems [228, 229]. Inactivation of the protozoan cysts and *Acanthamoeba* sp., disinfection of bacterial and viral pathogens, and controlling algal blooms using PDT are reported [230-234]. A 10  $\mu\text{M}$  concentration of the PS cationic porphyrin Tetra-Py<sup>+</sup>-Me and irradiation for 120 min using 40 W m<sup>-2</sup> artificial white light resulted in the 5 log CFU/100 mL reduction of *E. coli* in the waste treatment system [228]. The high concentration of suspended particles and heterogeneous chemical composition of wastewater may negatively influence the efficacy of PACT, which are currently addressed using high concentrations of PSs and long-time exposure to light. Therefore, technological advancements are required for the commercial applications of photodynamic disinfection in removing pathogenic microbes from sewage before disposing to natural ecosystems.

Photodynamic disinfection has potential application to drinking water purification, which will benefit those with limited access to clean water. Nearly 840 million people worldwide have limited access to clean/safe drinking water, and water-associated diseases such as cholera, dysentery, and polio are prevalent among a significant population, especially children [235, 236]. As per UNICEF reports, diarrhea was responsible for eight percent of all deaths among children under age five worldwide in 2017, translating into 480,000 per year. Assuring access to safe drinking water by 2030 has become the UN's sustainable development goal to prevent the spread of water-associated diseases [235]. PACT is a promising strategy that can be extended from a small scale in a bottle for individual use to a large scale in a treatment system to disinfect drinking water. Disinfection of poliovirus and bacterial pathogens in tap water using photodynamic disinfection was demonstrated in the early 1970s. The low efficacy of photodynamic disinfection in turbid waters due to light scattering and PS damage are major concerns in large-scale treatment systems [230, 232, 237]. Studies by Kuznetsova *et al.* proposed a four-stage system to resolve this issue. They demonstrated a photodynamic water treatment system at 200 L h<sup>-1</sup> at Rublevsk water treatment station, Moscow [238, 239]. The turbidity was removed in the first stage by sand filtration, followed by photodynamic disinfection and excess dye removal in the third stage using activated carbon adsorption. Mild chlorination also was applied in the fourth stage. Flowing water through columns containing immobilized PSs or floating immobilized PS columns in the treatment systems is the option to avoid PS leakage into the final water [240]. An immobilized PS is desirable, as it can be separated easily and reused in the batch scheme, and immobilized PSs have high photostability compared to free ones. In a recent development, Ugwuja *et al.* [236] proposed using bimetallic hybrid clay nanocomposites prepared by doping clay and *Carica papaya* seeds with Zinc and copper for effective photodynamic water disinfection for rural communities and developing countries. Recent studies also used PSs combined with natural sunlight to enhance the solar

disinfection of drinking water, validated from PET bottles to a large scale in several countries [241-243].

PACT is especially important for aquaculture, where the irrational use of antibiotics is widely reported and has contributed to the emergence of several bacteria resistant to commonly used antibiotics [244-246]. Although the implications of antibiotic applications in the aquaculture sector vary, such as the emergence of antibiotic-resistant pathogens, financial loss on detecting the antibiotic residues in the meat, and long-term environmental deterioration, farmers are still prompted to use such drugs. This tendency is due to farmers' lack of scientific awareness of the health hazards of antibiotics to humans and insufficient alternative tools to protect their crops from bacterial infections. PACT is a safe alternative to antibiotics to ensure quick bacterial disinfection without inducing damage to the host cells or developing antimicrobial resistance. However, the need for instrumentations and light sources for large-scale illumination, inaccessibility to kill internal pathogens, and a short lifetime of ROS are PACT's limitations for its application to aquaculture. PDT was found to induce the death of >50% of the cells of *Vibrio harveyi* within 10 min due to the ROS-mediated cell wall damage [22]. Other studies also demonstrated the inactivation of bacterial pathogens of aquatic organisms using PACT [72, 85, 247, 248], while the field level demonstration is not yet validated. It is a viable idea that the PACT or its combination with solar disinfection or ROS enhancers such as KI could find potential application in aquaculture hatcheries. Small photodynamic tanks would even help disinfect the ornamental fishes in aquariums.

## **Summary**

The concept of PACT for replacing antibiotics to kill microbial pathogens have progressed much in the last few decades from laboratory scale experiment to medical, environmental, coating and textile industries. PACT is demonstrated for its application to cure periodontal and skin infections and disrupt biofilms. The immediate action, reduced expense, and superiority over antibiotic resistance make PACT attractive. However, the lack of control over the specificity of photoreactions and reduced efficiency for deep tissue applications remain. The invention of novel amphiphilic photosensitizers and functionalized nanoparticles may enhance the PACT specificity and efficiency. Also, nontoxic chemicals like KI may improve ROS production and PACT efficiency. Little research is carried out on advancing light sources than photosensitizers, which is crucial for advancing PACT. The application of PACT in public health management is yet another promising concept, especially in the current scenario of the COVID-19 pandemic. Further, the importance of PACT principles in the

inactivation of bacterial pathogens in the sewage and drinking water systems is yet to be realized, which is promising by considering the crisis on the availability of quality drinking water.

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