

Applications of Antimicrobial Photodynamic Therapy

Subjects: Biochemistry & Molecular Biology | Pharmacology & Pharmacy

Contributor: Sandile Songca, Yaw Anane

Originally discovered as a relatively new anticancer therapeutic technology, photodynamic therapy (PDT) has since evolved and is now used in many therapeutic technologies. For example, it is used against viruses, such as the recently reported antiviral activity against COVID-19, bacteria, fungi, and parasites, in treating neovascular disease, in environmental sanitation and pest control, and in many other applications.

Keywords: biofilm ; planktonic bacteria ; extracellular polymeric substance ; antimicrobial photodynamic therapy ; antibiotic chemotherapy ; photothermal hyperthermia therapy ; magnetic hyperthermia therapy ; cold atmospheric pressure plasma ; sonodynamic therapy ; nanozyme enhanced

1. Introduction

Originally discovered as a relatively new anticancer therapeutic technology ^[1], photodynamic therapy (PDT) has since evolved and is now used in many therapeutic technologies. For example, it is used against viruses, such as the recently reported antiviral activity against COVID-19 ^[2], bacteria ^[3], fungi ^[4] and parasites ^[5], in treating neovascular disease ^[6], in environmental sanitation ^[7] and pest control ^[8], and in many other applications. Besides anticancer applications, photodynamic therapeutic applications against bacteria have defined the knowledge field of antimicrobial photodynamic therapy (aPDT) ^[9] and the allied healthcare variant known as photodynamic antimicrobial chemotherapy ^[10]. Common reference to both photodynamic antimicrobial chemotherapy and photoactivated chemotherapy (PACT) as antimicrobial chemotherapy is unfortunate because oxygen in the latter is not required ^[11]. PDT has been shown to kill many bacterial species in planktonic and biofilm formations ^{[12][13]}. Although aPDT photosensitizers have shown very little or no tendency to induce it ^{[14][15][16]}, some mechanisms of bacterial resistance have been reported, including ABCG2 mediated efflux, DNA damage repair, procaspase damage-induced inhibition of apoptosis, heat shock protein upregulation, hypoxia, and antioxidant defense mechanisms ^[17]. Given that biofilm formation is one of the most important mechanisms for the development of bacterial resistance, there has been increasing focus on the development of new methods for the treatment of bacterial biofilms ^[18], among which PDT has been highly prized with an increasing number of research reports showing promising results in vitro and in vivo ^{[19][20]}.

Furthermore, aPDT has been used in combination with several other therapeutic agents, with additive and synergistic efficacy enhancement ^{[21][22]}. aPDT combinations with chemotherapy have been studied for the potential treatment of bacterial infections ^[23]. Other combination therapy studies include PDT with anticancer chemotherapy ^[24], photothermal hyperthermia therapy (PTT) for anticancer applications ^[25], antibacterial applications ^[26], and antifungal applications ^[27]. PDT has also been studied in combination with magnetic hyperthermia therapy (MHT) for various applications including hard-to-reach cancers such as brain cancer ^[28] and bone tissue cancers ^[29]. As a therapeutic technology, MHT involves the temperature elevation of tissues in which embedded magnetic nanoparticles are energized using a high frequency alternating magnetic field generated by an appropriate MHT applicator ^[30].

When combined with cold atmospheric pressure plasma therapy (CAP), PDT has the potential to overcome hypoxia, which limits the concentration of reactive oxygen species that can be generated by PDT ^{[31][32]}. The reason for this is that CAP essentially introduces exogenous reactive gas species from a plasma jet (in the case of the direct CAP) or from a plasma activated fluid (in the case of the indirect CAP). When a gas such as helium or oxygen is passed over a high voltage electrode, reactive gas species are generated at room temperature in the gas phase, including high energy electrons and gas phase ionic species, creating a cold atmospheric pressure plasma gas as a controllable source of reactive species ^[33]. These reactive species are widely used to destroy undesirable cells directly or indirectly. Devices used in CAP include the dielectric barrier discharge device ^[34] PlasmaDerm® VU-2010 ^[35], the atmospheric pressure plasma jet kINPen® MED ^[36], and the SteriPlas ^[37], which are CE-certified as medical products to treat chronic wounds in humans with efficacy and a good tolerability.

2. The Microbial Biofilm Structural Challenge

Deeper understanding of the biofilm structure and how it contributes to antibiotic resistance has improved since the late 1970s [38], when they were first recognized in clinical samples. Biofilms are constituted from microbial communities that intimately associate with surfaces to sustain viability and improve their resistance up to a thousand times more than their planktonic forms; the surface contact and association is a key requirement for the biofilm formation mechanism [39]. Biofilms are characterized by an extensive multi-channel-permeated extracellular 3D matrix among the cells, consisting of polymeric materials, including polysaccharides and peptides, nucleic acids and lipids [40]. The biomolecule constitution of the biofilm matrix and extracellular polymeric substances (EPS) has been described in more detail [41]. It plays a vital role as a living environment for the bacterial cells in the biofilm [42] and as an infective mechanism through detachment and re-attachment [43]. Researchers have recognized several stages in biofilm formation, including contact and adhesion, formation of the colony, biofilm architecture maturation, final detachment and distal infection.

Therefore, bacterial biofilms enhance antibiotic resistance and further infection [44]. Furthermore, the formation of biofilm is a collective behavior that is triggered by cell-to-cell proximity and facilitated by a bacterial quorum-sensing mechanism [45]. Due to their importance for therapeutic strategy formulation, several studies on the physical, chemical and mechanical properties of biofilms such as substrate adhesion, adsorption of chemical substances, and admission of other cells, have been conducted [46][47][48][49]. These studies have revealed that antibiotics acting on their own do not alter the biofilm structure to gain sufficient access to the constituent bacterial community. Many of these properties can be exploited to overcome the formidable bacterial biofilm formation defense mechanism.

For example, their sessile nature may permit therapeutic targeting and imaging for precision drug delivery. The bacterial biofilm is a hydrophilic and wettable environment, amenable to aqueous soluble drugs and delivery strategies. Variable oxygenation levels have been reported, and the multi-channel 3D structure and reported hypoxia suggest limited susceptibility to the type II mechanism of PDT [50]. The chemical composition of the EPS of the biofilm may be among the key considerations for drug design and targeting strategies, because drugs and photosensitizers that bind to any of the known constituents of the EPS biofilm matrix could contribute toward biofilm structure disruption [51]. For these reasons, the affinity for biofilm penetration may be a key factor in therapeutic strategies.

3. Antimicrobial Photodynamic Therapy

In the aPDT approach, absorbed light energy is always used for bactericidal or bacteriostatic impact through two key molecular photosensitizer-mediated mechanisms. While the type I mechanism is based on radical-forming hydrogen transfer from a light energized photosensitizer directly to biomolecules, the type II mechanism involves an initial photosensitization of oxygen to produce reactive oxygen species, which in turn attack biomolecules [52]. The mechanistic basics of type I and type II may be illustrated using a Jablonski diagram as shown in **Figure 1**, showing the direct and the reactive oxygen species mediated pathways. Studies have shown that both mechanisms cause irreversible chemical reactions that alter the functionality of biomolecules and disrupt their environment [53], regardless of whether these biomolecules are cellular, EPS matrix components or other functional constituents of the biofilm [54]. These studies showed that aPDT is not prevented by the biofilm from achieving an increase in intracellular reactive oxygen species. At the same time, several studies have focused on the impact of aPDT on the biofilm matrix strength and constituent pathogen metabolic activity [55][56]. For example, bacterial pathogen reduction and eradication was found to be accompanied by reactive oxygen- induced oxidative stress, biofilm matrix weakening, loss of adhesion and component changes [57].

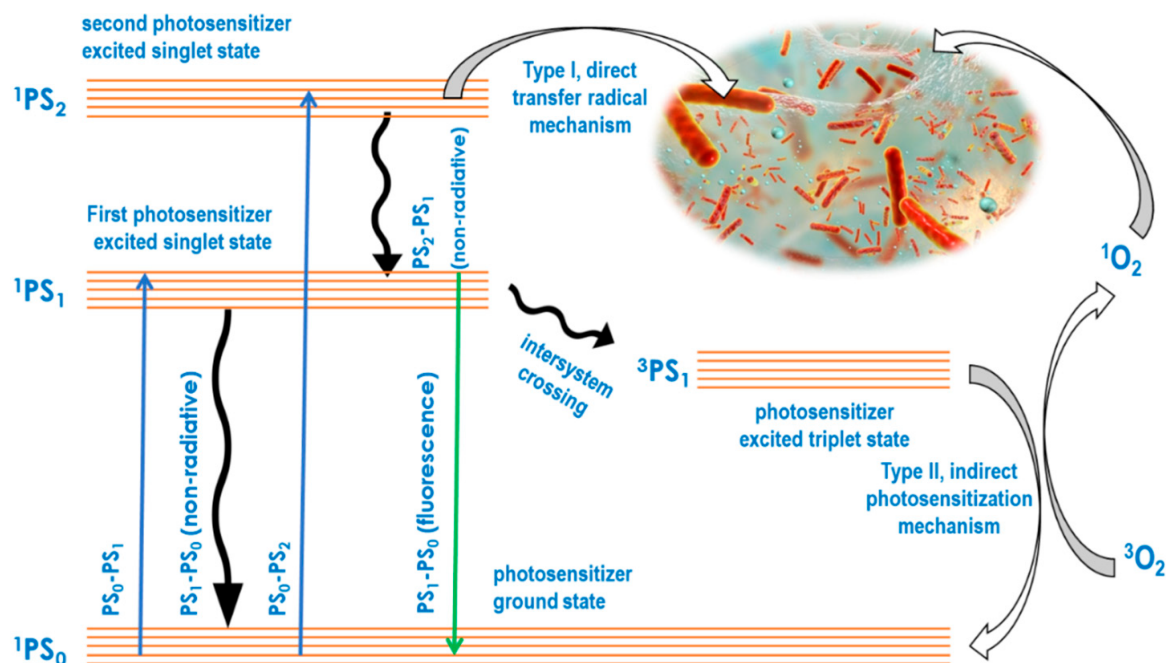


Figure 1. Jablonski diagram to illustrate the aPDT type I and II mechanisms.

Several aPDT studies have been conducted on the planktonic and biofilm forms of bacterial and fungal pathogens. Using aPDT for example, the planktonic and polymicrobial biofilms of methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa* and associated fungi were reduced to less than 99.99% using methylene blue as the photosensitizer and 670 nm laser light for excitation of the photosensitizer [58]. Additionally, aPDT completely eradicated Gram-negative *Moraxella catarrhalis* and Gram-positive *Streptococcus pneumoniae* in both their planktonic and biofilm forms using the photosensitizer Chlorin-e6 and 670 nm light for excitation of the photosensitizer [59]. Biofilm-forming *Acinetobacter baumannii* planktonic cells and biofilms were eradicated using methylene blue and protoporphyrin IX photosensitizers, illuminated at 652 nm for excitation of the photosensitizer [60]. These studies show that aPDT is effective in eradicating biofilm-forming bacterial strains in both their planktonic and biofilm forms. **Table 1** summarizes the methodologies, pathogens and impact of the six key studies discussed.

Table 1. Antibacterial photodynamic therapy alone.

Photosensitizer	Nanoconjugate System Used	Gram Negative	Gram Positive	Study Phase	Impact Target	Ref
polyethylenimine-chlorin(e6) and tris-cationic-buckminsterfullerene	dendrimer nanoconjugate	<i>E. coli</i> <i>P. mirabilis</i> <i>P. aeruginosa</i>	<i>S. aureus</i> <i>E. fecalis</i>	in vitro in vivo	biofilm + planktonic	[53]
1-oxo-1H-phenalen-2-yl methyl pyridinium chloride (SAPYR) and 1-oxo-1H-phenalen-2-yl-methyl-dodecan-1-aminium chloride (SA-PN-05)	None	<i>E. coli</i>	<i>A. naeslundii</i> <i>S. mutans</i>	in vitro	biofilm + planktonic	[54]
porfimer sodium (hematoporphyrin derivative)	None	<i>F. nucleatum</i>		in vitro	biofilm	[57]

Photosensitizer	Nanoconjugate System Used	Gram Negative	Gram Positive	Study Phase	Impact Target	Ref
Methylene blue	None	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>P. aeruginosa</i> , <i>S. marcescens</i> , <i>H. influenzae</i>	<i>C. albicans</i> , <i>E. faecalis</i> , <i>S. aureus</i> , <i>S. pneumoniae</i>	in vitro in vivo	biofilm	[57]
Chlorin-e6	None	<i>H. influenzae</i>	<i>M. catarrhalis</i> , <i>S. pneumoniae</i>	in vitro	biofilm + planktonic	[59]
Protoporphyrin IX and Methylene blue	None	<i>A. baumannii</i>		in vitro	biofilm + planktonic	[60]

References

- Diamond, I.; Granelli, S.G.; McDonagh, A.F.; Nielsen, S.; Wilson, C.B.; Jaenicke, R. Photodynamic therapy of malignant tumours. *Lancet* 1972, 2, 1175–1177.
- Svyatchenko, V.A.; Nikonov, S.D.; Mayorov, A.P.; Gelfond, M.L.; Loktev, V.B. Antiviral photodynamic therapy: Inactivation and inhibition of SARS-CoV-2 in vitro using methylene blue and Radachlorin. *Photodiagn. Photodyn. Ther.* 2021, 33, 102112.
- Ghorbani, J.; Rahban, D.; Aghamiri, S.; Teymouri, A.; Bahador, A. Photosensitizers in antibacterial photodynamic therapy: An overview. *Laser Ther.* 2018, 27, 293–302.
- Liang, Y.I.; Lu, L.M.; Chen, Y.; Lin, Y.K. Photodynamic therapy as an antifungal treatment. *Exp. Ther. Med.* 2016, 12, 23–27.
- Debora, P.; Aureliano, D.P.; Ribeiro, M.S.; Lindoso, J.A.L.; Pogliani, F.C.; Sellera, F.P.; Song, D.; Mauricio, S.; Baptista, M.S. Treatment and Control of Leishmaniasis Using Photodynamic Therapy, *Leishmaniasis-Trends in Epidemiology, Diagnosis and Treatment*; Claborn, D.M., Ed.; IntechOpen: London, UK, 2014.
- Newman, D.K. Photodynamic therapy: Current role in the treatment of chorioretinal conditions. *Eye* 2016, 30, 202–210.
- Brovko, L.Y.; Meyer, A.; Tiwana, A.S.; Chen, W.; Liu, H.; Filipe, C.D.; Griffiths, M.W. Photodynamic treatment: A novel method for sanitation of food handling and food processing surfaces. *J. Food Prot.* 2009, 72, 1020–1024.
- Shiao, S.-H.; Weng, S.-C.; Luan, L.; Vicente, M.D.G.H.; Jiang, X.-J.; Ng, D.K.P.; Kolli, B.K.; Chang, K.P. Novel phthalocyanines activated by dim light for mosquito larva- and cell-inactivation with inference for their potential as broad-spectrum photodynamic insecticides. *PLoS ONE* 2019, 14, e0217355.
- Cieplik, F.; Deng, D.; Crielaard, W.; Buchalla, W.; Hellwig, E.; Al-Ahmad, A.; Maisch, T. Antimicrobial photodynamic therapy-what we know and what we don't. *Crit. Rev. Microbiol.* 2018, 44, 571–589.
- Wainwright, M. Photodynamic antimicrobial chemotherapy (PACT). *J. Antimicrob. Chemother.* 1998, 42, 13–28.
- Farrer, N.J.; Salassa, L.; Sadler, P.J. Photoactivated chemotherapy (PACT): The potential of excited-state d-block metals in medicine. *Dalton Trans.* 2009, 48, 10690–10701.
- Cieplik, F.; Tabenski, L.; Buchalla, W.; Maisch, T. Antimicrobial photodynamic therapy for inactivation of biofilms formed by oral key pathogens. *Front. Microbiol.* 2014, 5, 405.

13. Vollmer, A.; Al-Ahmad, A.; Argyropoulou, A.; Thurnheer, T.; Hellwig, E.; Attin, T.; Vach, K.; Wittmer, A.; Ferguson, K.; Skaltsounis, A.L.; et al. Antimicrobial Photoinactivation Using Visible Light Plus Water-Filtered Infrared-A (VIS + wIRA) and *Hypericum Perforatum* Modifies In Situ Oral Biofilms. *Sci. Rep.* 2019, 9, 20325.
14. Liu, Y.; Qin, R.; Zaat, S.A.J.; Breukink, E.; Heger, M. Antibacterial photodynamic therapy: Overview of a promising approach to fight antibiotic-resistant bacterial infections. *J. Clin. Transl. Res.* 2015, 1, 140–167.
15. Sabino, C.P.; Wainwright, M.; Ribeiro, M.S.; Sellera, F.P.; dos Anjos, C.; Baptista, M.S.; Lincopan, N. Global priority multidrug-resistant pathogens do not resist photodynamic therapy. *J. Photochem. Photobiol. B Biol.* 2020, 208, 111893.
16. Al-Mutairi, R.; Tovmasyan, A.; Batinic-Haberle, I.; Benov, L. Sublethal Photodynamic Treatment Does Not Lead to Development of Resistance. *Front. Microbiol.* 2018, 9, 1699.
17. Casas, A.; Di Venosa, G.; Hasan, T.; Battle, A. Mechanisms of Resistance to Photodynamic Therapy. *Curr. Med. Chem.* 2011, 18, 2486–2515.
18. Hughes, G.; Webber, M.A. Novel approaches to the treatment of bacterial biofilm infections. *Br. J. Pharmacol.* 2017, 174, 2237–2246.
19. de Melo, W.C.; Celiešiūtė-Germanienė, R.; Šimonis, P.; Arūnas, S.A. Antimicrobial photodynamic therapy (aPDT) for biofilm treatments. Possible synergy between aPDT and pulsed electric fields. *Virulence* 2021, 12, 2247–2272.
20. Hu, X.; Huang, Y.Y.; Wang, Y.; Wang, X.; Hamblin, M.R. Antimicrobial Photodynamic Therapy to Control Clinically Relevant Biofilm Infections. *Front. Microbiol.* 2018, 9, 1299.
21. Pérez-Laguna, V.; Gilaberte, Y.; Millán-Lou, M.I.; Agut, M.; Nonell, S.; Rezusta, A.; Hamblin, M.R.A. A combination of photodynamic therapy and antimicrobial compounds to treat skin and mucosal infections: A systematic review. *Photochem. Photobiol. Sci.* 2019, 18, 1020–1029.
22. Vieira, C.; Gomes, A.T.P.C.; Mesquita, M.Q.; Moura, N.M.M.; Neves, M.; Graça, P.M.S.; Faustino, M.A.F.; Almeida, A. An Insight Into the Potentiation Effect of Potassium Iodide, on aPDT Efficacy. *Front. Microbiol.* 2018, 9, 2665.
23. Lee, H.J.; Kang, S.M.; Jeong, S.H.; Chung, K.H.; Kim, B.I. Antibacterial photodynamic therapy with curcumin and *Curcuma xanthorrhiza* extract against *Streptococcus mutans*. *Photodiagn. Photodyn. Ther.* 2017, 20, 116–119.
24. Lee, H.; Han, J.; Shin, H.; Han, H.; Na, K.; Kim, H. Combination of chemotherapy and photodynamic therapy for cancer treatment with sonoporation effects. *J. Control. Release* 2018, 283, 190–199.
25. Li, X.; Lovell, J.F.; Yoon, J.; Che, X. Clinical development and potential of photothermal and photodynamic therapies for cancer. *Nat. Rev. Clin. Oncol.* 2020, 17, 657–674.
26. Bilici, K.; Atac, N.; Muti, A.; del Valle, C.A.; Miravet, J.F.; Rezusta, A.; Galindo, F. Broad spectrum antibacterial photodynamic and photothermal therapy achieved with indocyanine green loaded SPIONs under near infrared irradiation. *Biomater. Sci.* 2020, 8, 4616–4625.
27. Rodríguez-Cerdeira, C.; Martínez-Herrera, E.; Fabbrocini, G.; Sanchez-Blanco, B.; López-Barcenas, A.; EL-Samahy, M.; Juárez-Durán, E.R.; González-Cespón, J.L. New Applications of Photodynamic Therapy in the Management of Candidiasis. *J. Fungi* 2021, 7, 1025.
28. Cramer, S.W.; Chen, C.C. Photodynamic Therapy for the Treatment of Glioblastoma. *Front. Surg.* 2020, 6, 81.
29. Matsubara, T.; Kusuzaki, K.; Matsumine, A.; Asanuma, K.; Nakamura, T.; Uchida, A.; Sudo, A. A Minimally Invasive Surgery for Bone Metastases Using the Combination of Photodynamic Therapy and Hyperthermia Treatment. *Int. J. Clin. Med.* 2013, 4, 357–363.
30. Liu, X.; Zhang, Y.; Wang, Y.; Zhu, W.; Li, G.; Ma, X.; Zhang, Y.; Chen, S.; Tiwari, S.; Shi, K.; et al. Comprehensive understanding of magnetic hyperthermia for improving antitumor therapeutic efficacy. *Theranostics* 2020, 10, 3793–3815.
31. Karami-Gadallo, L.; Ghoranneviss, M.; Ataie-Fashtami, L.; Pouladian, M.; Sardari, D. Enhancement of cancerous cells treatment by applying cold atmospheric plasma and photo dynamic therapy simultaneously. *Clin. Plasma Med.* 2017, 7, 46–51.
32. Wang, M.; Geilich, B.M.; Keidar, M.; Webster, T.J. Killing malignant melanoma cells with protoporphyrin IX-loaded polymersome-mediated photodynamic therapy and cold atmospheric plasma. *Int. J. Nanomed.* 2017, 12, 4117–4127.
33. Yan, D.; Xu, W.; Yao, X.; Lin, L.; Sherman, J.H.; Keidar, M. The Cell Activation Phenomena in the Cold Atmospheric Plasma Cancer Treatment. *Sci. Rep.* 2018, 8, 15418.
34. Balzer, J.; Heuer, K.; Demir, E.; Hoffmanns, M.A.; Baldus, S.; Fuchs, P.C.; Awakowicz, P.; Suschek, C.V.; Opländer, C. Non-Thermal Dielectric Barrier Discharge (DBD) Effects on Proliferation and Differentiation of Human Fibroblasts Are Primary Mediated by Hydrogen Peroxide. *PLoS ONE* 2015, 10, e0144968.

35. Brehmer, F.; Haenssle, H.A.; Daeschlein, G.; Ahmed, R.; Pfeiffer, S.; Görlitz, A.; Simon, D.; Schön, M.P.; Wandke, D.; Emmert, S. Alleviation of chronic venous leg ulcers with a hand-held dielectric barrier discharge plasma generator (PlasmaDerm®) VU-2010): Results of a monocentric, two-armed, open, prospective, randomized and controlled trial (NCT01415622). *J. Eur. Acad. Dermatol. Venereol.* 2015, 29, 148–155.
36. Bekeschus, S.; Schmidt, A.; Weltmann, K.-D.; von Woedtke, T. The plasma jet kINPen—A powerful tool for wound healing. *Clin. Plasma Med.* 2016, 4, 19–28.
37. Arndt, S.; Schmidt, A.; Karrer, S.; von Woedtke, T. Comparing two different plasma devices kINPen and Adtec SteriPlas regarding their molecular and cellular effects on wound healing. *Clin. Plasma Med.* 2018, 9, 24–33.
38. Rabin, N.; Zheng, Y.; Opoku-Temeng, C.; Du, Y.; Bonsu, E.; Sintim, H.O. Biofilm formation mechanisms and targets for developing antibiofilm agents. *Future Med. Chem.* 2015, 7, 493–512.
39. Muhammad, M.H.; Idris, A.L.; Fan, X.; Guo, Y.; Yu, Y.; Jin, X.; Qiu, J.; Guan, X.; Huang, T. Beyond Risk: Bacterial Biofilms and Their Regulating Approaches. *Front. Microbiol.* 2020, 11, 928.
40. Karygianni, L.; Ren, Z.; Koo, H.; Thurnheer, T. Biofilm Matrixome: Extracellular Components in Structured Microbial Communities. *Trends Microbiol.* 2020, 28, 668–681.
41. Amankwah, S.; Abdella, K.; Kassa, T. Bacterial Biofilm Destruction: A Focused Review On The Recent Use of Phage-Based Strategies With Other Antibiofilm Agents. *Nanotechnol. Sci. Appl.* 2021, 14, 161–177.
42. Flemming, H.C.; Neu, T.R.; Wozniak, D.J. The EPS matrix: The house of biofilm cells. *J. Bacteriol.* 2007, 189, 7945–7947.
43. Kaplan, J.B. Biofilm dispersal: Mechanisms, clinical implications, and potential therapeutic uses. *J. Dent. Res.* 2010, 89, 205–218.
44. Jamal, M.; Ahmad, W.; Andleeb, S.; Jalil, F.; Imran, M.; Nawaz, M.A.; Hussain, T.; Ali, M.; Rafiq, M.; Kamil, M.A. Bacterial biofilm and associated infections. *J. Chin. Med. Assoc.* 2018, 81, 7–11.
45. Dickschat, J.S. Quorum sensing and bacterial biofilms. *Nat. Prod. Rep.* 2010, 27, 343–369.
46. Renner, L.D.; Weibel, D.B. Physicochemical regulation of biofilm formation. *MRS Bull.* 2011, 36, 347–355.
47. Billings, N.; Birjiniuk, A.; Samad, T.S.; Doyle, P.S.; Ribbeck, K. Material properties of biofilms—A review of methods for understanding permeability and mechanics. *Rep. Prog. Phys.* 2015, 78, 036601.
48. Kesel, S.; Grumbein, S.; Gümperlein, I.; Tallawi, M.; Marel, A.K.; Lieleg, O.; Opitz, M. Direct Comparison of Physical Properties of *Bacillus subtilis* NCIB 3610 and B-1 Biofilms. *Appl. Environ. Microbiol.* 2016, 82, 2424–2432.
49. Feng, J.; Lamour, G.; Xue, R.; Mirvakili, M.N.; Hatzikiriakos, S.G.; Xu, J.; Li, H.; Wang, S.; Lu, X. Chemical, physical and morphological properties of bacterial biofilms affect survival of encased *Campylobacter jejuni* F38011 under aerobic stress. *Int. J. Food Microbiol.* 2016, 238, 172–182.
50. Wu, Y.; Klapper, I.; Stewart, P.S. Hypoxia arising from concerted oxygen consumption by neutrophils and microorganisms in biofilms. *Pathog. Dis.* 2018, 76, fty043.
51. Shrestha, A.; Kishen, A. Polycationic chitosan-conjugated photosensitizer for antibacterial photodynamic therapy. *Photochem. Photobiol.* 2012, 88, 577–583.
52. Calixto, G.M.F.; Bernegossi, J.; De Freitas, L.M.; Fontana, C.R.; Chorilli, M. Nanotechnology-Based Drug Delivery Systems for Photodynamic Therapy of Cancer: A Review. *Molecules* 2016, 21, 342.
53. Huang, L.; Xuan, Y.; Koide, Y.; Zhiyentayev, T.; Tanaka, M.; Hamblin, M.R. Type I and Type II mechanisms of antimicrobial photodynamic therapy: An in vitro study on gram-negative and gram-positive bacteria. *Lasers Surg. Med.* 2012, 44, 490–499.
54. Muehler, D.; Rupp, C.M.; Keceli, S.; Brochhausen, C.; Siegmund, H.; Maisch, T.; Hiller, K.A.; Buchalla, W.; Cieplik, F. Insights Into Mechanisms of Antimicrobial Photodynamic Action Toward Biofilms Using Phenalen-1-One Derivatives as Photosensitizers. *Front. Microbiol.* 2020, 11, 589364.
55. Kikuchi, T.; Mogi, M.; Okabe, I.; Okada, K.; Goto, H.; Sasaki, Y.; Fujimura, T.; Fukuda, M.; Mitani, A. Adjunctive Application of Antimicrobial Photodynamic Therapy in Nonsurgical Periodontal Treatment: A Review of Literature. *Int. J. Mol. Sci.* 2015, 16, 24111–24126.
56. Sharab, L.; Baier, R.E.; Ciancio, S.; Mang, T. Influence of Photodynamic Therapy on Bacterial Attachment to Titanium Surface. *J. Oral Implantol.* 2021, 47, 427–435.
57. Mang, T.; Rogers, S.; Keinan, D.; Honma, K.; Baier, R. Antimicrobial photodynamic therapy (aPDT) induction of biofilm matrix architectural and bioadhesive modifications. *Photodiagn. Photodyn. Ther.* 2016, 13, 22–28.

58. Biel, M.A.; Sievert, C.; Usacheva, M.; Teichert, M.; Balcom, J. Antimicrobial photodynamic therapy treatment of chronic recurrent sinusitis biofilms. *Int. Forum Allergy Rhinol.* 2011, 1, 329–334.
 59. Luke-Marshall, N.R.; Hansen, L.A.; Shafirstein, G.; Campagnari, A.A. Antimicrobial Photodynamic Therapy with Chlorin e6 Is Bactericidal against Biofilms of the Primary Human Otopathogens. *mSphere* 2020, 5, e00492-20.
 60. Anane, Y.A.; Apalata, T.; Vasaikar, S.; Okuthe, G.E.; Songca, S.P. In vitro antimicrobial photodynamic inactivation of multidrug-resistant *Acinetobacter baumannii* biofilm using Protoporphyrin IX and Methylene blue. *Photodiagn. Photodyn. Ther.* 2020, 30, 101752.
-

Retrieved from <https://encyclopedia.pub/entry/history/show/51931>