American Journal of Clinical Microbiology and Antimicrobials

Review Article
Published: 08 Nov, 2019

Phthalocyanines Derivatives as Control Approach for Antimicrobial Photodynamic Therapy

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Abstract

The ongoing enhanced resistances of pathogens against antibiotics frequently single mode of action are amongst one of the major clinical challenges that entail rapid and novel alternatives. Antimicrobial Photo Dynamic Therapy (APDT) is a feasible choice that manifests multiple target site action and predicted to proliferate in upcoming days. The photo sensitizers are activated during light visible wavelength spectra from 400 nm to 700 nm which in turn forms free radicals that immediately kills pathogens. This review summarized the newly synthesized photosensitizes such as phthalocyanines, porphyrins and phenothiazinium derivatives which are widely investigated. Zinc phthalocyanine conjugates establishing efficient binding, visible spectra, and investigation assured confiscating toxicity both *in vitro* and *in vivo* models. The Zinc phathalocyannine conjugated with pent lysine and conjugated with variable charges especially n^{+8} exhibited high inhibition towards multi drug resistance bacteria. Phthalocyanines get much more benefits on basis of industrial applications such as pigment dye used in fabric and manifested an enormous candidate for friendly environment. Similarly the concern materials depicting a booming stability along with their fabulous photochemical and photo physical properties in semiconductor, solar cells, optical data, sensors and photo catalysts and also demonstrating a vial therapy in the antimicrobial or antitumor applications. Photo antimicrobial therapy is gaining significant importance, as a new alternative that could slow the pace of resistance development in pathogens. However, the global and national authorities should provide proper funding, market space and should have the courage to practice.

Keywords: Pathogen; Antimicrobial Photodynamic Therapy (APDT); Photosensitizer; Phenothiazinium; Chromospheres

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Received Date: *27 Sep 2019*

Accepted Date: *30 Oct 2019*

Published Date: *08 Nov 2019*

Citation:

Ahmad A, Hayat A, Rahman MU, Khan J. Phthalocyanines Derivatives as Control Approach for Antimicrobial Photodynamic Therapy. Am J Clin Microbiol Antimicrob. 2019; 2(3): 1041.

Introduction

The ongoing enhanced resistance of pathogens against antibiotics is amongst one of the fundamental and major clinical challenges [1]. Pathogens almost dominated maximum of the current era antibiotics in co-evolutionary race owing to high rate of random mutation and rapid recombination [2]. The six superbugs pathogen i.e. *Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and *Enterobacter strains* shows high level of resistance to any single kind or narrow spectrum antibiotic [1]. In last few years, various clinical reports, health and global experts and governments declared that pathogens become capable of rapidly developing resistance against those antibiotics, having single mode of action and that, antibiotics are no more presumed to overwhelm the challenge, worldwide. Thus, it is risky to left the public in danger like in post-antibiotic era to treat their general transmittable infections ECDC surveillance report 2012, ECDC surveillance report 2015, European commission staff, 2015 [1]. The situation enforced infectious disease society of America, WHO, G7 summit, European commission, and governments of developed countries in accord to call for alternative clinical practices and the urgent development of novel antimicrobial strategies to overcome the rapid and broad spectrum resistance of pathogens. To overcome the situation Welcome trust and UK Department of Health reported that US is spending on antimicrobial resistance programs a sum of USD 2 billion as advanced funding in 2014 [3]. Never the less, the US amount is USD 1.2 billion (US CDC, 2016). A new broad spectrum antibiotics teixobactin have been developed which carry the potential to attack at multiple and alternative target sites. However, the antibiotic just inhabit gram positive bacteria and further more rapid, harmless, effective and novel antimicrobial approaches likely having multiple target site against resistance development are required to control many other most virulent pathogens such as gram negative bacteria, mycobacteria, fungi, viruses and

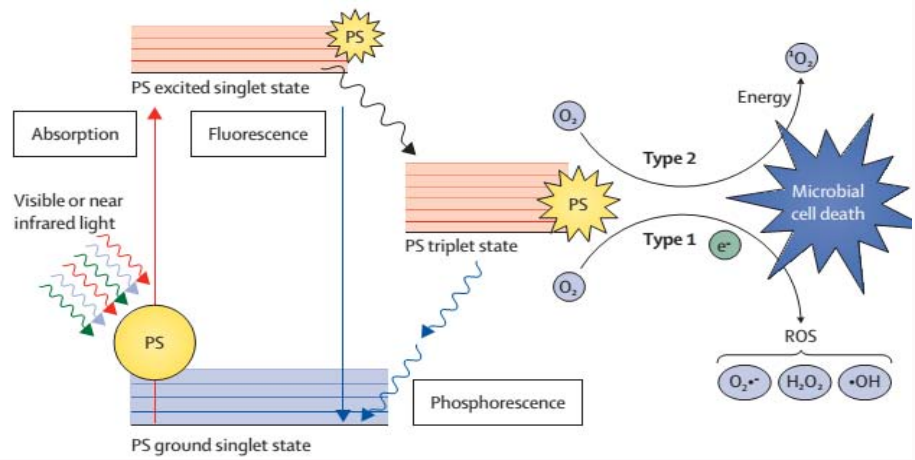

Figure 1: Mechanism of action of antimicrobial photosensitizes.

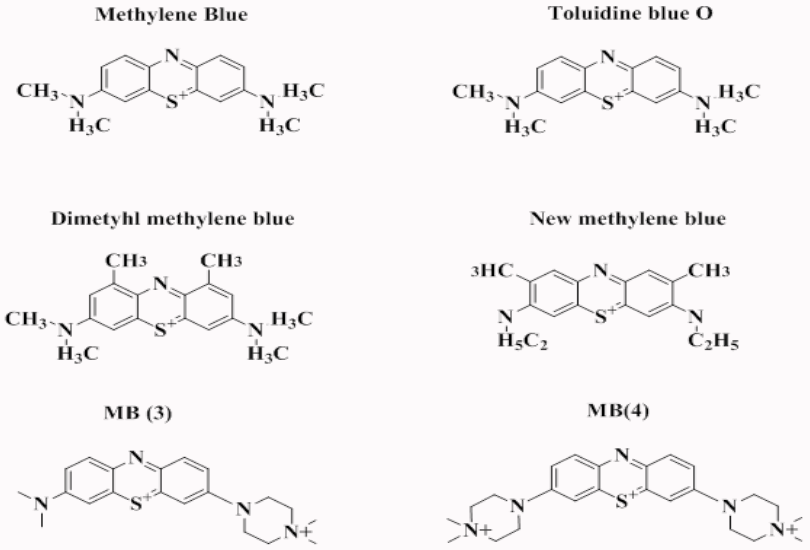

Figure 2: Chemical structures of new developed phenothiazinium dyes.

protozoans [4,5]. Antimicrobial Photo Dynamic Therapy (APDT) is a feasible choice that manifests multiple target site action. Tumor targeted photo dynamic therapy is being used since more than twenty five years but APDT is mostly not acknowledged among clinician and health authorizes for health care provision [6,7]. Recently, the increasing rate of novel photo antimicrobial agents and their clinical trials make APDT as more safe and efficient. Here we reviewed the current antimicrobial novel approaches, advancement, their clinical trials, uses and prospects for adoptions.

Antimicrobial Photosensitizer

Photosensitizer plays an important role in inhibition against various virulent pathogens. The photosensitizes are activated during light visible wavelength spectra from 400 nm to 700 nm which in turn forms free radicals that immediately kills pathogens [8]. Photo antimicrobial agents, chemical oxidations disrupt and inhibit virulent factor of microbes such as proteases, toxin, sphingomylinase, lipopolysaccharides, and α-haemolysin expression [9,10]. Antioxidant enzymes activate transcription factor against ROS, however, it is well documented that protein are susceptible to photosensitizer and definitely the antioxidant enzymes superoxide dismutase and catalases are also inactivated by photo antimicrobial approach. The β-lactamase and New Delhi metallo β-lactamase-1 of the drug resistant bacteria (*S. aureus, E. coli* and *K. pneumonia*) also shows susceptibility towards photosensitizer [11,12]. Photo antimicrobial agents also damage sophisticated phenotypic process of biofilm formation which shows resistance against multi drugs [12,13]. Penetration of light to tissues and microbes improves with wavelength of light. Several photosensitizers, based on phthalocyanines, porphyrins, phenothiazinium etc, so far have been produced, assessed and applied in antimicrobial photodynamic therapies and tumor photodynamic therapies around the globe that shows strong absorptions in the deep red spectral regions. In general, the anticancer photosensitizers tends to have lipophilic with little or no charge and typically have extended wavelength but the photo antimicrobial distinct cationic charges and in various case more charges enhanced the better binding efficiency to pathogens. However, well organized and selective binding of the photosensitizer to such infectious pathogens is one of major challenge for its success. The photosensitizers could be managed to the loci of infection such as lung, ear, nose and throat gastrointestinal tract, and urinary tract etc. endoscopically using fiber-optic technology, however, for more

deep infection transcutaneous needle is used to delivered both PS and light [14].

Mechanism of Photo Antimicrobial Action

The generation of Reactive Oxygen Species (ROS) can follow two alternative pathways after light activation by a given Photo Sensitizer (PS). The PS can absorb a photon in the ground state, forming the excited singlet state. This state can undergo intersystem crossing to a longer lived triplet state that might interact with oxygen by two mechanisms: in type 1) the generation of $O_2^{\bullet-}$, $^{\bullet}OH$, and H_2O_2 by electron transfer from the excited PS; in type 2) the triplet state of the PS can directly undergo energy exchange with triplet ground state oxygen, leading to the formation of excited $1O_2$. The generated ROS rapidly react with their environment depending on the localization of the excited PS e.g. microorganism cell walls, lipid membranes, peptides, and nucleic acids (Figure 1). The PS returns to its initial state after this cycle, ready to absorb a new photon and generate additional ROS. $O_2^{\bullet-}$= Superoxide anions; $^{\bullet}OH$= Hydroxyl radical, H_2O_2= Hydrogen peroxide, $1O_2$= Singlet oxygen, e^-= Electron.

Toxicity

Basically antimicrobial photosensitizers are not toxic molecules and should not be puzzled with biocides. The singlet oxygen molecules production rate of a single photosensitizer molecule is very high before its destruction due to their photo catalytic performance, as compare to the biocides the antimicrobials photosensitizers with low concentration can kill microbes more quickly, simple clinical management *via* controlling the intensity. What's more, the common specification for new intercessions to overwhelm the antibiotic resistance, resistance and infection preventing, available antibiotics preservation, resistance deceleration, and microbial attacking treatment developing with depreciate potential to drive resistance satisfied by photo antimicrobials.

Optimization Strategy of Leading Photo Sensitizers (PS)

Since 1903 different classes of photosensitizers were developed for an efficient photodynamic inactivation of both bacteria and fungi. The most appropriate photosensitizers are positively charged, water soluble and photo stable. In this section the most prominent photosensitizers are introduced.

Phenothiazinium Chromophore

Methylene Blue (MB) and Toluidine Blue (TBO) are two old school photosensitizers which belong to the chemical group of phenothiazinium characterized by a heterocyclic aromatic structure (Figure 2). Both molecules are well-known photosensitizers which have demonstrated efficient killing activity against a wide range of microorganisms. An overview can be found elsewhere [15]. Nevertheless MB was optimized by several groups to further enhance the Protein Disulfide Isomerase (PDI) efficacy. Therefore MB was substituted with methyl-groups (dimethyl methylene blue), ethyl-group (new methylene blue) or a nitro-group (methylene green) [16-18]. Felgentrager et al. [19] showed that additional cationic charges (primary, secondary and tertiary ammonium residues) in methylene blue derivatives (MB3 & MB4) lead to a better PDI efficiency. The PDI efficacy of these MB derivatives was improved from primary to secondary to tertiary ammonium residues. The authors stated better polarity characteristics of these MB derivatives by the use of these functional groups facilitating a better attachment of even uptake by the bacteria. In another study additional positive charges or hydrogen bond acceptors on symmetrically substituted phenothiazinium molecules were investigated [20]. The focus in this study was that positive charges were added on both sides of the core group of methylene blue. Again an improved antibacterial photodynamic effect was observed of these new derivatives compared to the parent molecule MB. Besides the development and optimization of MB derivatives for a PDI, a new mechanism of action of light-activated phenothiazinium dyes was hypothesized [21,22]. A potentiation of the PDI effect of these light activated dyes was observed mediated by addition of azide ion. Actual this observation is paradoxical, because sodium azide (NaN_3) is known as a quencher of $1O_2$. Here NaN_3 potentiated a Fenton-reaction mediated killing of Gram-positive and Gram-negative bacteria related to a more type-I mechanism of action. A possible explanation of these findings is the generation of an azidyl radical which is formed from NaN_3 and HO. Although azide radicals are less reactive than hydroxyl radicals they may survive longer to penetrate deeper in bacterial cells. In this case weak reactive or less effective means strong effective in inactivation of bacteria, because the azidyl radical lives long enough to penetrate inside the bacteria for targeting relevant target structures which leads immediately to a loss of function of proteins, enzymes or other bacterial structures. Therefore the killing of bacteria is enhanced and not quenched. Selection of new developed methylene blue derivatives DMB, NMB, MB and MB compared to MB or TBO [17,19,20]. In general porpyhrine dyes and phthalocyanines are aromatic macro cyclic compounds (Figure 3). The chemical core group is composed of tetra pyrrole-subunits interconnected *via* methane bridges. It is known that light activated meso-substituted cationic porphyrins kill bacteria independently of additional number of positive charges [23]. However one positive charge is a must have to inactivate especially Gram-negative bacteria. In addition Alves et al. [24] demonstrated that the number of positive charges directly correlates with an enhanced a PDI efficacy. Three and four positive charges showed the best photodynamic inactivation. A further idea for optimization of appropriate photosensitizers like TMPYP ($C_{72}H_{66}N_8O_{12}S_4$) was to increase the length of N-alkyl groups from methyl up to 14 CH_2 groups (C_nH_{2n}+1) which facilitate a better binding to the outer cell wall areas of bacteria [25]. This observation was correlated with an escalated growth inhibition upon light activation of these PS. However elongation of the alky chain from C_{18} to C_{22} did not further improve the amount of TMPYP dyes bound to bacteria. Recently TMPYP without any side-chain modification showed a very fast and effective a PDI efficacy using short light pulses of 100 ms for activation [26]. In this study a photodynamic inactivation rate of colony-forming unit (CFU) of >5 log 10 steps could be achieved within a total treatment time of a few seconds. Another porphyrins derivative XF_{73} demonstrated a high antibacterial photodynamic efficacy (Figure 2). Here the two positive charges (tri-methyl-ammonium) were arranged symmetrically and separated by a propyl-spacer (-C_3H_7) from the tetra pyrrol-ring system [27]. Such a spacer might provide a higher flexibility of the positive charge and therefore again a better interaction with the outer cell wall areas of bacteria. Next to the porphyrins cationic water-soluble Zn-phthalocyanines have also shown photodynamic inactivation of both Gram-negative and Gram-positive bacteria [28,29].

Phthalocyanine

Phthalocyanine is a resourceful class of macrocyclic compounds that gathering significance and interest because it possess great potential among other photosensitizer, as influential and second

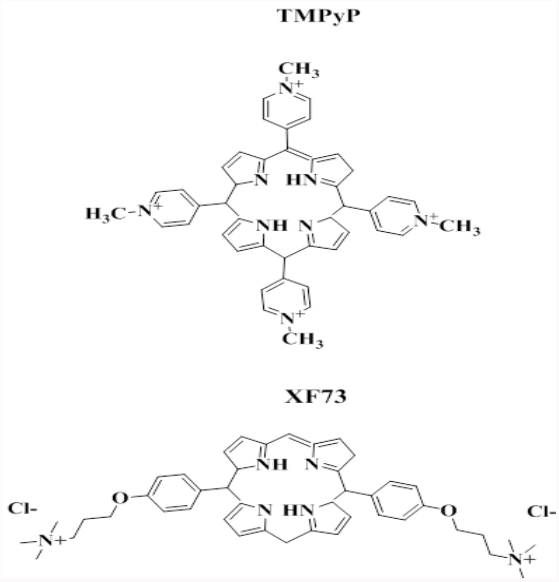

Figure 3: Chemical structures of TMPYP and XF73 [27].

generation photosensitizer in targeted photodynamic therapy [30,31]. Phthalocyanine is imperative in PDT due to its extended and visible wavelength of 600 nm to 700 nm [32]. Phthalocyanine without substitution are unable to be used in a PDT while conjugated with positive charge make it effective against bacteria because positive charged phthalocyanine efficiently bind to bacterial cell wall that having negative charge [24]. Diverse numbers of metal Phthalocyanines have been developed [33]. To produce high frequency of ROS, several Metallic Phthalocyanines (MPCs) with diamagnetic elements such as Silicon (Si), Aluminum (Al) and Zinc (Zn), have been established Nyokong. Zinc phthalocyanine is a successful metallic antimicrobial agent due to its little poisonousness, unique photo physiological characteristics (owing high penetration in the red area (two times greater than in blue area) of visible spectrum 650 nm to 800 nm), higher molar extinction coefficient and good (0.67) singlet oxygen quantum yield and other photochemical and chemical stability as compared to other phthalocyanines [34,35]. Activating and linking photo-sensitizer with positive charge enhances the interaction with lipo-polysaccharides, lies at the outer wall of gram positive bacteria. Different zinc phthalocyanine conjugated with bio-molecules have been reported and actively tested against several disease causing pathogens.

Derivatives of Zinc Phthalocyanine and its Applications

Zinc Phthalocyannine polylysine conjugate

Conjugating antimicrobial peptides to ZnPcs is a vigorous approach to kill pathogens. In the earlier of this running decade, a novel zinc phthalocyanine combined with poly lysine amino acids (ZnPcs-PL) has been reported (Figure 4A) and tested against periodontitis in comparison with chlorin-e6-polylysine (Ce6-PL). The substituted ZnPcs-PL photosensitizer considerably deactivated periodontitis bacteria which were 100 times higher than control using qRT PCR load. To check the toxicity and selectivity of ZnPcs-PL photosensitizer in cell lines of human periodontal ligament cells or mammalian bone morrow stem cell 4 μm ZnPcs-PL was exposed to 18 J/cm light intensity and manifested high selectivity of ZnPcs-PL for Porphyromonas gingivalis [36]. Zinc phthalocyanine conjugated with heptalysine amino acid was found highly efficient against stomach adeno carcinoma [37].

Zinc phthalocyanine pentalysine conjugate

Another, substituted compound of zinc phthalocyanine was designed by conjugating with penta-lysine amino acid (ZnPc-$(Lys)_5$) (Figure 4B). Chemically this cationic photo-sensitizer derivative carries positive charge, under physiological pH and is soluble in water. (ZnPc-$(Lys)_5$ binds tightly to bacteria having negative charge. Application revealed ZnPc-$(Lys)_5$ meaningfully high uptake amount and quicker uptake by P. gingival is compared to Tetra Sulfonate zinc phthalocyanine (ZnPc-S_4) and ZnPc-COOH. Further, *in vitro*, and *in vivo*, application of ZnPc-(Lys) 5 at concentration (1-20 μm) against Gram negative bacteria significantly killed bacteria at 670 nm compared to control ZnPc-S_4 [38]. ZnPc-$(Lys)_5$ was also tested *in vitro* and in animal model against bacterial skin infection. Different concentration (10^{-7}m, $10^{-6.5}$m and 10^{-6}m) of ZnPc-$(Lys)_5$ was exposed to LED with light dosage at 680 nm for 1 to 2 min. Result showed high antibacterial ability of the conjugate ZnPc-$(Lys)_5$ .The researchers further found anti inflammation activity of ZnPc-$(Lys)_5$ by reason of that ZnPc-$(Lys)_5$ significantly declined the blood flow of the wound skin [39]. Recently, ZnPc-$(Lys)_5$ (of concentration 0.3 μm, 1 μm and 3 μm) was also tested using household light against *E. coli*. Result indicated that an exposure of bacterial pathogen to red LED (660 nm, with a light fluence of 0.15 J/cm^2) for two seconds significantly killed 80% of *E. coli* [40]. Additionally, illumination of ZnPc-$(Lys)_5$ with laser light showed strong inhibition towards tumor cell in mice [40].

Zinc phthalocyanine variable positive charged ($ZnPc(TAP)_4^{n+}$) conjugate

A novel macrocyclic compound of Zinc phthalocyanine conjugated with variable positive charges ($ZnPc(TAP)_4^{n+}$), where n=0, 4, 8, 12 was recently designed (Figure 4E). Variable positive charged revealed that among the series of compounds, conjugate with 8 positive charges at light intensity of 5 J/cm^2 with concentration of 59 nm showed robust antibacterial effect against *E. coli*. However, $ZnPc(TAP)_4^{12+}$ showed high level of binding to bacteria than

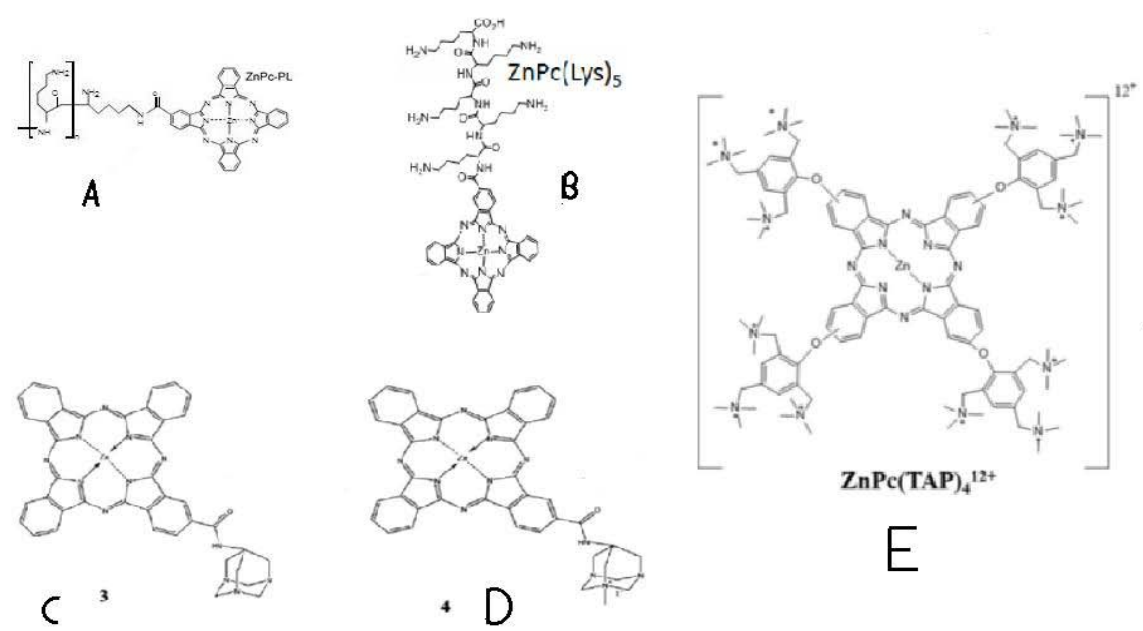

Figure 4: Structure formula of Zn-Phthalocyannine derivatives. **A)** Zinc Phthalocyannine-polylysine (ZnPc-PL) [37] **B)** Zinc Phthalocyannine-pentlysine $ZnPc(Lys)_5$ [38] **C)** Zn (II) phthalocyanine mono-substituted with a triazatricyclodecane moiety (compound 3) [42] **D)** Zn (II) phthalocyanine mono-substituted with cationic *N*-methylated derivative (compound 4) [42] **E)** Zinc Phthalocyannine with variable charges n=0, 4, 8, 12 (Here $N=^{12+}$) [31].

$ZnPc(TAP)_4^{8+}$ and also exhibited 1000 fold decrease in drug resistant *E. coli* at 1 µm with light intensity 4.5 J/cm^2. All PCs using flow cytometry revealed that they are fast binder and saturate within 5 minutes. $ZnPc(TAP)_4^{4+}$, and $ZnPc(TAP)_4^{8+}$ produced free radical by both type I and II while $ZnPc(TAP)_4^{12+}$ just create ROS through type I. This novel conjugates of ZnPc was reported as non toxic [31].

β-Carboxy phthalocyanine zinc with lanthanide-doped up conversion nano-particles and polyvinyl pyrrolidone

UCNPs-CPZ-PVP (β-carboxy phthalocyanine zinc, CPZ) delivery system with lanthanide-doped up conversion nano-particles and Polyvinyl Pyrrolidone (PVP) *in vitro* and *in vivo* analysis showed high efficacy against drug resistance bacteria i.e. *aureus* and *E. coli.* UCNPs-CPZ-PVP also exhibited high efficiency against antifungal strain of *Candida albicans* [41].

Zn(II) phthalocyanine mono-substituted with triazatricyclodecane and N-methylated

Zn(II) phthalocyanine triazatricyclodecane (Figure 4C) showed strong Photo toxicity towards Gram positive bacteria while N-methylated compound (Figure 4D) showed strong inhibition towards Gram negative and positive bacteria. The N-methylated derivative of Zn(II) phthalocyanine revealed 99.99% eradication of *E. coli* and *S. aureus* strains of bioluminescent bacteria at 12.7 cm^2 concentration of the compound at wavelength of 670 nm [42].

Porphyrins

Porphyrins are aromatic macrocyclic tetra pyrrole structures conjugated through methane bridges. Porphyrins are efficiently activated by soret band at 400 nm. Q bands extended up to 630 nm reveal that porphyrins are very rarely activated in red light *in vivo* [43]. It is believed that porphrins meso-substitued positive charge eradicates pathogens sovereign of extra positive charges on porphyrins, during light activation. But, one positive charge is essential to bind to Gram negative bacteria [23]. However, it was later reported that increasing additional positive charges (3 to 4) on porphyrins are correlated with PDT efficiency [24]. To enhance the binding efficiency to outer cell wall regions of bacteria of porphyrins a new photosensitizer (TMPYP) was synthesized by growing the chain with the addition of alkyl group from methyl up to 14-CH_2 groups. Yet, furthermore elongating the chain from 18-CH_2 to 22 -CH_2 did not additionally enhance the binding efficiency of PS towards bacteria. Upon light activation these TMPYP up to 14-CH_2 groups revealed high level of inhibition to bacteria Reddi et al. [26] one more synthesized TMPYP lacking any branching chain by activating through short light impulses exhibited effective antimicrobial efficiency the photodynamic inactivation rate was very fast and within few seconds. Another derivative of porphyrins XF_{73} with two symmetrical positive charges (tri-methyl ammonium) separated by a propyl spacer from the tetra pyrrole ring of porphyrins manifested high aPDT efficacy. The spacer provides flexibility to positive charge enhancing the binding efficiency to pathogens cell wall [27]. Newly synthesized, cationic porphyrins derivatives revealed 99.9999% inhibition at different energies densities towards multidrug resistant *E. coli* from clinical sample [44].

Phenothiazinium Salt

The phenothiazinium salt has two common old school dyes i.e. Toluidine blue and Methylene blue are heterocyclic aromatic compounds [45,46]. The two dyes and their derivatives are generally researches against pathogenic microbes and anticancer [47,48]. Toluidine blue O Phenothiazinium compound is clinically used which show absorption at 660 nm in red light against wounds, burns, diabetic ulcer, periodontitis, and carious dentin lesion. Methylene blue which showed broad spectrum inhibition at 660 nm to chronic sinusitis, Methicillin resistant *S. aureus* surgical site, halitosis, periodontitis, oral candidiasis, oral mucositis, severe sepsis and septic shocks, and onychomycosis are also clinically registered to treat diseases [47,49-51]. Methylene blue was optimized by several schools to augment

their antimicrobial photodynamic therapy. Methylene blue was conjugated with dimethyl methylene blue and ethyl group and green methylene blue (nitro group). Synthesizing new methylene derivatives with improved polarity by substituting positive charges facilitate and enhance the better attachment and uptake of derivatives by pathogens which lead to better antimicrobial photodynamic therapy efficiency [19]. In another study, a new symmetrical phenothiazinium molecule was studied with extra cationic or hydrogen bond acceptor on both sides. The enhanced antimicrobial activity of this new methylene blue derivative was detected related to methylene blue [20].

Applications of PS in Other Areas to Overcome Pathogens Prevalence

One of the major cause of drug resistance evolution in pathogens is their transmission within hospitals is daily routine among patients. New strategies and interest are fundamental for pathogens control and prevalence in hospitals. Recently, a two layered ε-polylysine and mono-substituted β-carboxy phthalocyanine zinc was synthesized. The ε-polylysine was the bottom layered and use it positive charge against microbes. The fabric coat is washable and showed strong efficiency against Gram negative and Gram positive reducing the survival of *E. coli* and *S. aureus* 99% and 98% respectively [52]. PCs also play an important role in the disease treatment in veterinary e.g. caseous lymphadenitis of sheep is triggered by bacteria *Corynebacterium pseudotuberculosis* causing death, wool loss and an economic loss. A PDT demonstrated as substitute treatment because it cured caseous lymphadenitis within 15.3 days on average than control and also manifested no sign of reappearance in the treated nodes till six months [53]. Diverse range of tetra pyrrole photosensitizers with varied cell targeting, and localization properties have been structurally modified with variety of conjugates to augment the efficiency against cancer [30]. Similarly, food borne and waterborne diarrheal sickness put to death 2.2 million peoples around the world (WHO, 2016). Photosensitizer curcumin conjugated with Polyvinyl Pyrrolidone (PVP-C) and NovaSol® curcumin was sprinkled for refining chicken meat, peppers, and cucumber from drug resistance *S. aureus* at 50 μm and 100 μm at 33.8 J/cm^2. A PDT revealed 1.7 $\log_{10}$ (98%), 2.5 $\log_{10}$ (99.7%) and 2.6 $\log_{10}$ (99.8%) for chicken meat, pepper and cucumbers reduction in MRSA without any changes to these food stuff [54,55]. In short, photo-sensitizers are gaining multidisciplinary field importance.

Conclusion

We have already been victim of huge loss and down many because of these diseases causing microbes whereas still oppose persistent and extensive resistances development from such pathogens against conventional antibiotics. The recently, updated page on November 26, 2018 of CDC which reveal that data extracted from threat report 2013 enumerate four microbes (*Clostridioides difficile,* Carbapenem-resistant, *Enterobacteriaceae* (CRE), Drug-resistant *Neisseria gonorrhoeae*) as urgent threat, 12 (*Acinetobacter* multi drug resistant, *Campylobacter* drug-resistant, Fluconazole-resistant Candida, extended-spectrum β-lactamase producing *Enterobacteriaceae*, *Enterococcus* vancomycin-resistant, *Pseudomonas aeruginosa* multidrug-resistant, *Salmonella* (Drug-resistant non-typhoidal), *Salmonella* (Drug-resistant *Serotype Typhi*), Drug-resistant *Shigella,* Methicillin-resistant *Staphylococcus aureus* (MRSA), Drug-resistant *Streptococcus pneumoniae* and Drug-resistant Tuberculosis) as serious threat and three (Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-Resistant Group A *Streptococcus,* Clindamycin-resistant Group B *Streptococcus*) pathogens as concerning threat in United States. All the 19 microbes show resistance against antibiotics (CDC 2013). Just using conventional antibiotics, we should adopt diverse alternatives to beat pathogen resistance. The worldwide health organizations have called the need of novel alternative strategies (CDC 2013). Yet, no alternative tactics have been reported that has the potential to produce a parallel idea in the way wherein we address diseases triggered by microbial infections. Though, the remarkable performance of the PS is usually neglected in doubt of toxicity towards host. Toxicity to host cell is certainly being a challenge for any new antimicrobial agent, antibiotics or else in practical. Many of the newly synthesized photosensitizers such zinc phthalocyanine conjugated with penta-lysine and zinc phthalocyanine conjugate with variable charges especially n^{+12} assured confiscating toxicity to host eradicated most of the multi drug resistant microbes both *in vitro* and *in vivo*. A PDT work at much lower concentration to eradicate pathogens and the dose of light is controlled as clinically directed and additionally in localized infections; the PS should be locally administered to the infested region. However, only three photosensitizers indocyanine blue, toluidine blue O and methylene blue to date got usual medical endorsement. In a nutshell, we should not be narrow in investigating alternatives against antimicrobial agent but should search for diverse range of approaches to beat pathogens resistance. Photo-antimicrobial therapy gaining importance, as new alternative that could slow the pace of resistance development in pathogens. However, the authorities, on the other hand, should provide proper funding, market space and should have the courage to practice.

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