Photosensitizers in antibacterial photodynamic therapy: an overview

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Antibacterial Photodynamic therapy (APDT) is a process utilizing light and light sensitive agents (named photosensitizer (PS)) and is usually applied in an oxygen-rich environment.
The energy of the photons is absorbed by the photosensitizer and subsequently transferred to surrounding molecules. Consequently, reactive oxygen species and free radicals are formed. These oxidative molecules can damage bacterial macromolecules such as proteins, lipids and nucleic acids and may result in bacterial killing. Unlike antibiotics, APDT as a novel technique does not lead to the selection of mutant resistant strains, hence it has appealed to researchers in this field.
The type of PS used in APDT is a major determinant regarding outcome. In this review, various types of PS that are used in antimicrobial Photodynamic therapy will be discussed. PSs are classified based on their chemical structure and origin. Synthetic dyes such as methylene blue and toluidine blue are the most commonly used photosensitizers in Antibacterial Photodynamic therapy (APDT). Other photosensitizers including natural PSs (e.g. curcumin and hypericin) and tetra-pyrrole structures like phthalocyanines and porphyrins have also been studied. Furthermore, nanostructures and their probable contribution to APDT will be discussed.

Key words: Antimicrobial photodynamic therapy • Photosensitizer • Nanostructures • APDT • Nano-structure • Curcumin • Porphyrins • Toluidine blue • methylene blue

A pinch of history

Phototherapy began in ancient Egypt. Ancient Egyptians treated some skin diseases with herbs and sunlight. They applied natural photosensitizers such as psoralens (extracted from particular plants such as Parsley and St-john's-wort) for treatment of leprosy lesions [1, 2].

Osar Raab, a medical student who worked in Munich was the first one to notice that dyes like acrydine along with light can kill paramecia. He discovered that the incubation of paramecium with acridine and consequent exposure to light potentially kills paramecium. However, the mere application of acridine without light exposure was not effective [3]. In following years, Von Tappeiner coined the term "photodynamic action" and attested that the presence of oxygen is essential in photodynamic action.

The first PDT was performed on a patient with skin carcinoma. It was carried out by T. Appaeiner and H. Jesionek in 1904. They used Eosin as PS along with white light. In recent years, more advances have been made in anticancer photodynamic therapy and different PSs are discovered [1, 2, 4, 5].

Antibacterial Photodynamic Therapy (APDT) was first introduced in 1960. Macmillan used toluidine blue against microorganisms like bacteria, algae, and yeast. It was observed that 99% of bacteria were killed within 30 min of irradiation with 21-30 mW of light at 632 nm from

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a continuous-wave gas laser. A few years later, researchers found that toluidine acts on cell membrane [6]. Other dyes including methylene blue, rose Bengal, eosine Y, neutral red, acridine orange, crystal violet and rhodamine 6G were presented as a photosensitizer and it was established that cationic dyes are more effective against bacteria than anionic PS [7]. Cationic molecules carry a positive charge on their functional groups, so they are easily bound to and taken up by bacteria which possess negative charge on the surface. However, the discovery of penicillin and its miraculous bactericidal properties, as well as other antibiotics impeded the progresses made in APDT.

In April 2014, WHO warned that we are on the cusp of a "post-antibiotic era". The growing resistance to many antibiotics in recent years and emergence of multidrug-resistant bacteria has diverted the attention towards alternative antibacterial therapies such as APDT.

Advantages of APDT over antibiotics:

Recent studies strongly uphold the hypothesis that APDT can be a satisfactory alternative since there is a substantial difference in the mode of action of PSs than that of antibiotics. The key benefits of APDT can be outlined as follows:

- A broad spectrum of action compared to antibiotics since PS can act on diverse organisms such as bacteria, protozoa, fungi;
- Bactericidal effects independent of antibiotic resistance pattern;
- More limited adverse effect profile and damage to the host tissue;
- No resistance following multiple sessions of therapy.

Mechanism of action:

Photodynamic therapy utilizes PS along with visible or ultraviolet light to produce cytotoxic singlet oxygen and free radicals which exert detrimental effects on microorganisms. PSs possess a stable electronic configuration which is set at the lowest or ground state level.

After irradiation at a certain wavelength, the PS is promoted from the ground state to an excited state. In other words, electrons relocate to higher energy orbitals. This singlet state is unstable with a half-life between 10^{-6} and 10^{-9}. These electrons are liable to lose their excess energy and return to ground state by emitting light (i.e. fluorescence) or heat. Moreover, Changes in electron spins can also shift the molecule to the triplet state. This process is known as "intersystem crossing" [8].

The triplet state PS reacts with the substrate in two different pathways- type I and type II [9]. Type I reaction involves electron transfer from triplet state PS to an organic substrate within the cells, leading to the production of free radicals. These free radicals interact with oxygen in molecular level and produce reactive oxygen species (ROS) such as superoxide, hydroxyl radicals and hydrogen peroxide. These oxidizing molecules potentially react with bacterial biomolecules and harm them.

In Type II reaction, energy transfer occurs between the excited PS and the ground-state molecular oxygen, producing singlet oxygen that can interact with a large number of molecules in the cell to generate oxidized products **(Fig. 1)**. The ratio of the occurrence between these two types is dependent on the type of PS that is used and the environment in which APDT is applied.

In this review, we will describe different types of

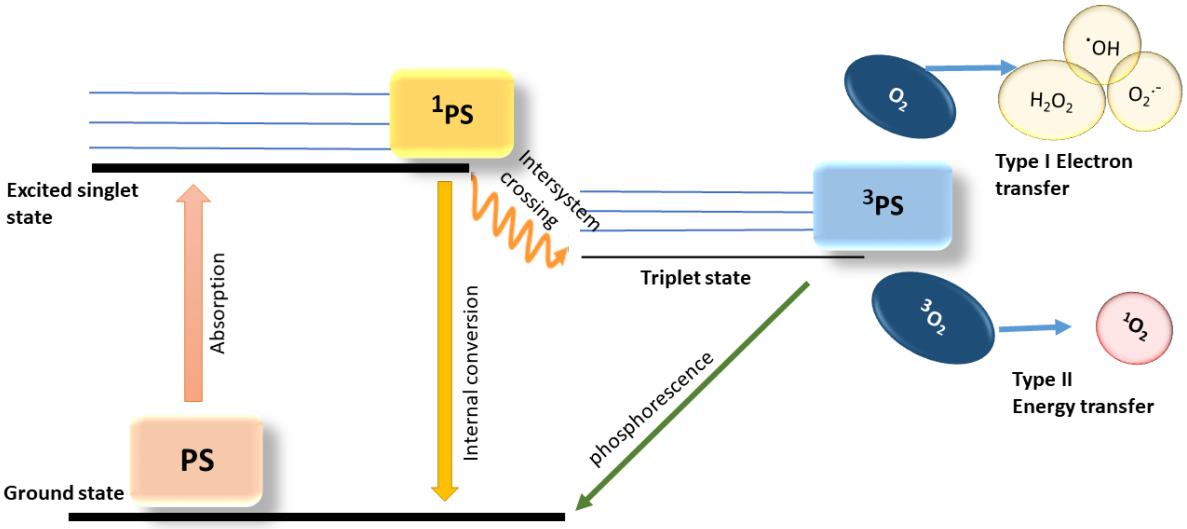

Fig. 1: Graphical illustration of type I and type II photochemical mechanisms of PDT PS, ground state photosensitizer; ^{1}PS, PS in first excited state; ^{3}PS, triplet state PS; .OH, hydroxyl radical, O_2.-, superoxide anion; $^3O_2$, triplet state oxygen

photosensitizers which are used in APDT. PSs used in APDT are classified into four groups based on their structure and origin; synthetic dyes, tetra-pyrrole structures, natural PSs and nano-structures.

Synthetic Dyes

Phenothiazinium is a subgroup of synthetic dyes. The most commonly used phenothiazinium dyes are methylene blue (Mb) and toluidine blue (Tb) **(Table 1)**.

These dyes were the first generation of PSs that were investigated for anticancer PDT. However, because of their cationic charge, they tend to bind to both gram-negative and gram-positive bacteria with high affinity, thus nowadays they are mainly used in APDT in clinical settings [10].

Many published studies have determined that phenothiazinium PSs such as MB and TB are effective on planktonic bacteria. Furthermore, some studies also tested the efficacy of phenothiazinium against biofilm structures.

Fontana et al. added MB on *ex vivo* poly-microbial biofilms of dental plaque samples obtained from patients with chronic periodontitis. MB (25-50 µg/ml) and biofilms were incubated for 5 min and then diode laser (665nm) was applied. It was observed that PDT led to the inactivation of 63% of bacteria present in suspension but killed only 32% of bacteria in the biofilm. The conclusion was reached that bacteria in biofilm structure have lower susceptibility than planktonic bacteria because of the low penetration of PS into the biofilm [11].

Phenothiazines possess intrinsic cationic charge that makes them effective against many bacteria. To improve their function, some moieties like methylation can be introduced. Wainwright et al. found that functionalization of methylene blue by adding methyl group led to increasing singlet oxygen production and greater photo-inactivation [12]. The effect of additional positive charges on the antimicrobial activity of the photosensitizer has been investigated. For example, Felgentrager et al. showed that functionalization of MB with tertiary ammonium increased both attachment and uptake by Gram-positive

Table1: commonly studied PSs and their photodynamic properties, *: Enterohemorrhagic E. coli

class	example	charge	Excitation maximum	Sample (bacteria)	Concentration of PS	Overall efficacy	Ref
Phenothiazinium	Methylene blue	cationic	632nm	Dental plaque samples	25 µg/ml	8%	(11)
	Toluidine blue	cationic	410nm	*S. mutans*	100 mg/l	2-5 $\log_{10}$	(77, 78)
				E. coli	35 µM	0.08 $\log_{10}$	
	Rose Bengal	anionic	532nm	*E. faecalis*	10 µM	4 $\log_{10}$	(79)
				P. aeruginosa		3 $\log_{10}$	
	Dimethyl methylene blue	cationic	635-652nm	*A. baumannii*	200 µM	2 $\log_{10}$	(80, 81)
	New methylene blue	cationic	635-652nm	*A. baumannii*	800 µM	3.2 $\log_{10}$	(80, 81)
Natural PSs	Curcumin	neutral	547nm	*S. mutans*	0.75 to 5 g/l	≥ 3 $\log_{10}$	(41, 42)
				L. acidophilus			
	Hypericin	neutral	593nm	*S. aureus*	100 nM	4-5 $\log_{10}$	(82-84)
				E. coli	1 µg/ml	≤ 0.2 $\log_{10}$	
	Flavin derivatives	cationic	450nm	MRSA	50 µM	5.1 $\log_{10}$	(85)
				EHEC*	50 µM	6.5 $\log_{10}$	
Tetra-pyrrole structures	Porphyrin	cationic	446nm	*S. aureus*	10 µM	1-2 $\log_{10}$	(32, 86, 87)
				P. aeruginosa	225 µM	4 $\log_{10}$	
				E. faecalis	100 µM	No effect	
	Phthalocyanine	Neutral	670nm	*A. hidrophila*	2 mM	≤ 0.5 $\log_{10}$	(22)
	Zink Pc derivatives	Cationic	690 nm	*S. aureus*	64 ng/ml	5-6 $\log_{10}$	(88-90)
				P. aeruginosa	26 µg/ml	5-6 $\log_{10}$	
	Chlorine	Neutral	660nm	*S. aureus*	10 µg/ml	5 $\log_{10}$	(91)
				E. coli	5 µg/ml	0.75 $\log_{10}$	
	Chlorine	Cationic	532nm	*E. coli*	5 µg/ml	0.77 $\log_{10}$	(92)
Nano structures	Fullerenes	neutral	532nm	*S. aureus*	1 µg/ml	3 $\log_{10}$	(93, 94)
				E. coli		≥ 85%	
	Titanium dioxide	neutral	near-UV light (400)	Water treatment	1 mg/ml	77-93%	(95)

and Gram-negative bacterial cells, because these substituents have a greater cationic charge than the secondary ammonium substituents [13].

Other synthetic dyes are Eosin Y, Erythrosine (ERY) and Rose Bengal (RB) which belong to anionic xanthene dyes derived from Fluorescein. All these dyes have an absorption peak in the green wavelength range (480-550 nm). The attachment and uptake of anionic PSs by the bacterial cells are lower than cationic PSs [14].

Kishen et al. compared the efficacy of a cationic PS (MB) and an anionic PS (RB) on inactivate biofilms of *E. feacalis*. APDT with MB was superior to RB in regard to cytotoxic effects on *E. feacalis*. They also showed that applying a specific microbial efflux pump inhibitor like verapamil hydrochloride along with MB photodynamic therapy enhances the destruction of biofilm [15].

It has been noted that sometimes bacteria can decrease the effects of PS. The bacterial efflux pumps decrease the concentration of Phenothiazinium dyes in bacterial cells [16, 17]. This decreased concentration buys time for the antioxidant machinery of the bacteria to activate, resulting in less inactivation. Tegos et al. have demonstrated that efflux pump inhibitors such as NorA and MexAB inhibitors increase the photo-inactivation of TB in *S. aureus* and *P. aeruginosa* [18].

Recently, new derivatives such as dimethyl methylene blue (derived from MB) and EtNBS (N-ethylpropyl-sulfonamido) have been studied. These dyes possess a high cationic charge that makes them more effective against bacterial cells [19-21].

Tetrapyrrole Structures

Tetra-pyrroles are one of the largest and firstly introduced PSs groups. Tetra-pyrrole structures have been named "pigment of life" because of their abundancy in nature (e.g. in hemoglobin or chlorophyll). There are numerous tetra-pyrrole compounds that are used as PSs in PDT, whereas porphyrins and phthalocyanines are the most frequently used PSs in APDT.

Phthalocyanines

Peak absorption of phthalocyanines is in the red region at 670 nm. Phthalocyanines (Pc) are diverse. Among these agents, Zinc phthalocyanine (ZnPc) is the most studied Pc for APDT.

Native ZnPc holds an affinity for gram-positive bacteria while its effectiveness against gram-negative bacteria is debatable **(Table 1)**. This phthalocyanine, if used in conjunction with cationic and anti-membrane agents such as polymyxin or EDTA (ethylenediamine-tetraacetic acid) can become effective against gram-negative bacteria.

Later studies have shown that the functionalization of Pc with cationic groups improves the binding affinity to bacterial cells and there is no need for polymyxin or EDTA [22, 23]. Dei D et al. discovered that water-soluble octa-cationic zinc Pc is efficacious against both gram-negative and gram-positive bacteria. Furthermore, the presence of eight positive charges thwarts the aggregation of phthalocyanine, unlike native compounds [24].

Cationic ZnPcs can also eliminate *E. coli* from blood products, making it advantageous in sterilization [25]. No study has been done concerning the use of PC in the clinical setting.

Porphyrin

Advantages like high frequency, high rate of ROS production and easy chemical modification makes Porphyrins one of the most commonly used PSs. Their absorption is in 405-550 nm range. Like other PSs, the presence of cationic charge is a very important factor in APDT [26].

Some bacteria tend to accumulate a large number of porphyrins making them susceptible to killing when irradiated with blue light or UV. Some anaerobic bacteria like *Propionibacterium acnes* and *Bacteroides* species and also oral bacteria including *Porphyromonas gingivalis*, *Prevotella* spp, and *Aggregatibacter actinomycetemcomtans* which produce black pigment fall under this category [27, 28, 29]. These bacteria with endogenous PS can be killed by mere light irradiation. Thus we can use APDT without PS administration for the treatment of Acne Vulgaris caused by *Propionibacterium acnes* [30, 31].

Cationic porphyrins like TMPyP (1-methyl-4-piridium-tetra(p-toluensulfonate)) have fourfold positive charge. Collins et al. used TMPyP against *Pseudomonas aeruginosa* biofilms both wild and mutant strains. Following the irradiation with mercury vapor lamp (400nm) for 10 min, they observed about 4 $\log_{10}$ steps inactivation for both strains [32]. In contrast, Fabian C et al. found no reduction of CFU at all when they used TMPyP against biofilms of *E. faecalis*. It was postulated that this effect might be due to the large molecular structure of TMPyP or strong electrostatic interaction between the fourfold positive charge of cationic porphyrin and negative charge of extracellular polymeric substance (EPS) molecules [33].

Nowadays cationic antimicrobial peptides or cell penetrating peptides are conjugated to porphyrins to improve their efficiency. These conjugated porphyrins show a great cell inactivation during APDT.

Natural PSs:

There are many natural compounds extracted from plants and other organisms which act as a photosensitizer and absorb white light or UV-A. Lots of natural PS compounds are yet to be discovered, hence the variety cannot be restricted. However, they hitherto include coumarins, furanocoumarins, benzofurans, anthraquinones and flavin derivatives **(Table 1)**. Hypericin and curcumin are two natural compounds that have been extensively stud-

ied as a photosensitizer over the years.

Hypericin

Hypericum perforatum or St John's-wort is a flowering plant which is traditionally known for its healing effects on burns and skin injuries. According to clinical studies, this plant also demonstrates antiviral, antidepressant, antibacterial and antitumor characteristics. Nonetheless, the mechanisms through which these effects are exerted have not been totally understood [34]. Hypericin is an anthraquinone derivative isolated from *Hypericum perforatum*. The best absorption of hypericin occurs at a wavelength of 600 nm which is sensed as orange-colored light.

It has been shown that hypericin-mediated APDT renders gram-positive bacteria including *Streptococci mutants*, *Lactobacilli mutants*, and *Propionibacterium acnes* inactivated [35]. Garcia et al. designed a study to determine the photoactivity of hypericin against clinically isolated gram-positive methicillin-sensitive, methicillin-resistant *Staphylococcus aureus* (MRSA) and *E. coli* producing gram-negative extended spectrum ß-lactamases (ESBL) [36].

The effectiveness of hypericin-mediated APDT on gram-positive MSSA and MRSA was significant, on the other hand, gram-negative *E. coli* was not susceptible to hypericin. It can be hypothesized that this difference in susceptibility to APDT is due to different cell wall structure that affects hypericin uptake. In fact, anionic and neutral PS tend to bind to gram-positive bacteria rather than gram-negative bacteria. Therefore, development of noble cationic hypericin derivatives will probably enhance the effectiveness of APDT against gram-negative bacteria.

Curcumin

Curcumin is another natural PS isolated from the root of a plant called *Curcuma longa*. Its optimum absorption is in the range of 405-435 nm. Curcumin executes a series of biological and pharmacological functions of which the following can be numerated: anti-oxidant [37] anti-inflammatory [38] anti-microbial [39] and wound healing [40] properties. Although quite a few studies have addressed these functions, the exact mechanisms are yet to be explored. The anti-inflammatory property of the curcumin makes it a favorable PS for treatment of periodontal diseases.

In all animal studies and a number of cell cultures, it has been established that curcumin is a rather safe compound regarding toxicity. Most studies about curcumin in the past 20 years are done in regard to its anticancer effects. However, recent publications report that curcumin is capable of inhibiting drug-resistant bacterial strain by means of photo-inactivation effect [42]. *S. aureus* is one of the most common resistant bacteria to antibiotic therapy which remains susceptible to curcumin-mediated inactivation [43].

Curcumin has demonstrated some antibacterial properties in absence of irradiation by binding to FtsZ proteins (homologs of eukaryotic cytoskeletal tubulin) and inhibiting the assembly of FtsZ protofilament in *Bacillus subtilis* [44].

In addition, curcumin seems to inhibit the transcription of *mecA* gene, leading to a reduced PBP2α expression which in turn causes ß-lactam antibiotics act more efficiently. As stated before, curcumin is also considered to be a photosensitizer for PDT as well as these favorable effects [45]. Najafi et al. compared the antimicrobial activity of curcumin and chlorhexidine digluconate (CHX)(as the gold standard mouthwash) against *Aggregatibacter actinomycetemcomitans* (one the main culprit bacteria in periodontal diseases) using curcumin (5 mg/ml), LED (120 J/cm^2) and CHX (2%). They concluded that curcumin is an effective substance in preventing the growth of *A.actinomycetemcomitans*, whose impact is reinforced when used simultaneously with PDT [41].

In terms of photo-killing effects, studies indicate that curcumin is 300 times more effective against the gram-positive *S. aureus* than the gram-negative *E.coli* and *Salmonella typhimurium* [46]. It must be noted that curcumin is also photo-labile during its photodynamic action and is rapidly photodegraded.

In order to overcome the poor water solubility and the rapid decay of the natural curcumin at physiological pH, Winter S et al. examined the applicability of polyvinylpyrrolidone curcumin (PVP-C) at the 50 micro-molar PVP-C (15 or 25 min incubation) and as a result, a complete eradication of *S. aureus* was achieved [47].

Nanostructures

During the last decade, nanotechnology has had a great impact on PDT. Most of these studies have used nanoparticles to improve the efficacy of anti-cancer PDT while a few of them have been done on the antimicrobial aspects [48].

Nanoparticles are utilized in diagnostic approaches and the delivery of non-water-soluble PSs or anionic PSs. This is done through encapsulation and subsequent improvement in photo-interaction and photo-inactivation.

The results with nanoparticles were more satisfactory than with the PS alone. Distribution of the ROS accounts for this disparity as the ROS produced by PS-nanoparticles was locally concentrated while with the free PS it was uniformly distributed in the medium, hence less efficient. Furthermore, PS bound to a nanoparticle penetrates through the membrane better than free PS.

Some nanostructures such as gold nanoparticles, carbon nanotubes, silica nanoparticles and up-conversions have been used in PDT [49]. Fullerenes and some quantum dots belong to another group of nanostructures and they act as a PS themselves [50].

The most commonly used classification of nanostructures and its coupling to PDT is proposed by Chatterjee et al. This classification includes active nanoparticles (nanoparticles applied as PS) and passive nanoparticles which are themselves divided into biodegradable (e.g. liposomes) and non-biodegradable nanoparticles like gold particles [51].

In this review, we describe four different types of interaction between nanoparticles and PS which are used in APDT processes. This classification has been proposed by Stefano Perni et al. and it includes; PS embedded in nanoparticles, PS bound to the surface of nanoparticles, PS-accompanying nanostructures and Nanoparticles as the PS [52].

1. PS embedded in nanoparticles

The majority of nanoparticles have been used as delivery vehicles for PSs such as tetrapyrroles, natural products, and phenothiazinium dyes.

Nanoparticles loaded with PS are primarily based on lipids such as liposomes and micelles, but sometimes carbohydrates like cyclodextrins are used as the basis for nanoparticles.

1-1. Liposome

Lipids exhibit the tendency to spontaneously aggregate in an aqueous environment and form bilayer structures. A well-known structure of this type is a liposome. Liposomes are nanosized vesicles composed of phospholipid and cholesterol and they are frequently used as carriers for PS [53].

There are two ways of incorporating PS into liposomes. First, as for water-soluble hydrophilic PS, it gets suspended in an aqueous environment with other compounds and then locates in the center of the liposome.

Second, non-water soluble hydrophobic PS dissolves in the hydrophobic environment and leads to the production of a liposome that contains the PS within the lipid bilayer. [54]

To optimize the liposome for APDT, cationic lipids like N-[1-(2,3-dioleoyloxy) propyl]-N, N, N-trimethylammonium methylsulfate (DOTAP) or DL-α-dipalmitoyl-phosphatidyl-choline can be affixed to the structure. Cationic liposomes are more effective than anionic or neutral ones in antibacterial photodynamic therapy because they can interact with the negatively-charged bacterial cell wall [55]. Furthermore, the encapsulation by liposome prevents PS aggregation which in turns results in an increased photo-inactivation effect [56]. In some occasions, an extra layer or another substance is added to modify the liposome charge. For instance, the use of calcium phosphate in the core of liposome leads to an increased effect against *P. aeruginosa* [57].

Nisnevitch et al. examined the effect of three water-soluble PSs including MB, Neutral Red (NR) and RB in their free form and encapsulated in liposomal formulations on both Gram-positive bacteria such as *S. aureus, Sarcina luteaa* and *S. epidermidis* and gram negative bacteria like *E. coli, K. pneumonia, P. aeruginosa, Salmonella para B* and *Shigella flexneri*. It was established that MB and NR enclosed in liposomal structures seem to have a greater antimicrobial effect than free PS for both Gram-positive and gram negative bacteria, whereas encapsulation of RB led to no intensification in its activity. Ultimately, it was suggested that encapsulation of PS can increase its deleterious effects on bacteria [58].

1-2. Micelles

Micelles fall under another category of nanoparticles that can incorporate PSs. They have been extensively used to deliver hydrophobic drugs by either entrapping or binding.

Some colloids can spontaneously form these nano-structures under certain conditions (with particle size 5-100 nm). Micelles are smaller in size than liposomes which results in more effective treatment. Besides, they are cheaper and easier to prepare. These unique properties, as well as increased permeability through the biological barriers and good drug bio-distribution, guarantee the widespread use of micelles compared to other nanoparticles [59, 60].

Tsai T et al. tested antimicrobial activity of hematoporphyrin (Hp) enclosed in either liposomes and micelles. The PDT efficacy was evaluated by means of the observed sensitivity of Gram-positive pathogens such as MSSA, MRSA, *S. epidermidis* and *Streptococcus pyogenes*. The results indicated that PDT with Hp encapsulated in micelles was more effective than the one encapsulated in liposomes at the same Hp doses [61].

2. PS bound to the surface of nanoparticles

PS bound to the surface of nanoparticles enhances the antimicrobial properties of PS. Several studies have been performed that report different PSs tend to bind to different nanoparticles. For example, porphyrin has a tendency for carbon nanotubes [62] while TB tends to bind to the surface of Au (Aurum) nanoparticles [63] and etc.

In this segment, we are going to explicate TB and its affinity for Au nanoparticles.

Since gold nanoparticle does not have any functional groups on the surface, direct attachment of TB molecules to gold is not possible, so a resurgence of reactive groups on the surface of nanoparticles is essential for absorption and binding of PS to the gold.

Functionalizing the gold with tiopronin is the most common approach to produce TB-Tiopronin-Gold nanoparticles. Jesus et al. compared the effect of TB-Tiopronin-Gold nanoparticles and free TB on the viability of *S. aureus*. The efficacy of TB-Tiopronin-Gold nanoparticles was four times greater than free TB [63, 64].

A different approach which proposed by Suci et al. is applying of a viral protein cage as a delivery vehicle of PS. Genetic construct of the viral protein cage had two benefits; site-specific targeting (by using Antibodies) and superior inactivation of bacterial cells [65].

3. PS-accompanying nanostructures

Sometimes nanoparticles cannot penetrate the bacterial membrane because of their considerably big size. On these occasions, it is plausible to keep the encased PS next to microbial cells. There are different mechanisms to achieve this goal.

Some studies have employed PSs in the polymer matrices such as silica and the others used nanoparticles like up-conversions [66] or quantum dots [67] in the proximity of PSs.

Confinement of TB and MB to silica matrix prevents the interaction between PS and microbial cell. During irradiation, produced ROS radicals moved away from the silicon and exerted their effect on neighboring microbial cells. With this approach, there was no need for adding PS again.

Biodegradable matrices such as silica can entrap many different PSs and result in monodisperse distribution and provide antimicrobial activity for a longer period of time. Due to the permeability of matrices to ROS and other types of molecular radicals, these molecules can easily migrate through the matrix, come out and kill bacteria. In addition, PSs inside the matrices are stable in pH changes and are not subject to microbial attack [49, 68].

Quantum dots (QD) such as CdSe and ZnS improve the effectiveness of PS in APDT. These molecules absorb the photons with certain energies (wavelength less than 480nm) and emit photons with longer wavelengths (approximately 642 nm). In this mechanism, the energy of light with appropriate wavelength is transferred to a neighboring PS via QD [69].

Recent studies have suggested that graphene quantum dots (GQD) can be used without PS. graphene is a single layer of carbon atoms forming a hexagonal lattice [67, 70]. Wen-Shuo et al. used GQD as the photosensitizer with two-photon absorption on *S. aureus* as a Gram-positive and *E. coli* as a Gram-negative bacterium. Both types of bacteria started to decrease during a 10-s irradiation [71].

Up-conversion is a process in which nanoparticle absorbs two or more photons followed by the emission of a shorter wavelength photon. While commonly applied in cancer PDT, this method has not hitherto been used in APDT [66].

4. Nanoparticles themselves act as PS

Fullerenes are acknowledged to be one of the most important nanoparticles that can act as PS. Other nanoparticles in this group are semiconductors [72]. Fullerenes display a spheroidal structure composed of pentagonal and hexagonal rings that consist of C_{60}, C_{70}, C_{84}.etc [73]. Lipophilic structure and neutral charge of these compounds account for their poor bactericidal effect. Modifications can be made with different cationic compounds.

Studies on *E. coli* in vitro about APDT showed that cationic fullerene N,N-dimethyl-2-(40-N,N,N-trimethyl-aminophenyl) fulleropyrrodinium iodide ($DTC60_{2+}$) hindered *E. coli* proliferation about 3.5 log_{10} after 30 min of irradiation under white light compared to the negligible killing effect of non-charged N-methyl-2-(40-acetamidophenyl) fulleropyrrolidine (MAC_{60}) [74]. The high selectivity and efficacy of this PS warrant the need for further investigations.

Alcohol functionalized fullerenes are not effective enough while other cationic fullerenes exhibited dark toxicity [73].

Semiconductors or photocatalysts like Titanium oxide(TiO_2) and ZnO are materials with semi-conduction properties. After irradiation with UVA, the electron in the valence band gets excited and shifts to the conductance band. This electron can produce ROS. TiO_2 nanoparticles are not used in the medical setting because of their absorption is in the UV range. With sunlight being the light source, TiO_2 nanoparticles are dominantly used for the disinfection of water and obtaining hygienic clean water. [75]. To make them applicable in clinical practice, researchers have focused their attention on shifting the absorbance spectrum of TiO_2 from UV region to visible light through doping with other elements [76].

Conclusions and future

The treatment of infections by means of APDT is a new revolutionary method and faces some challenges which need to be addressed. The most important limitation that must be confronted is the delivery of light and PS to the sites of infection. The use of PDT in infection is restricted to the location of the impaired part of the body on which the light must be administered. Body cavities and skin due to their easily accessible location and localized nature are feasibly treated with light. Therefore, antibacterial PDT is probably more efficient against localized diseases as opposed to systemic infections like sepsis and bacteremia. PS should selectively target microbes and leave out the intact tissue and this is one of the most important challenges which often has been solved by functionalization of PS. Functionalization with cationic moieties also increases the effect of PS on both Gram-positive and Gram-negative bacteria. The advent of nanostructural material, especially those with polymeric or liposomal formulations has been promising regarding some of the challenges like hydrophobic nature of some PSs which diminishes the efficacy of PS applied. The covalent attachment of hydrophilic polymer chain to the PS with low-molecular-weight and the solubilization of PS in lipo-

some carriers has been a great help. Nowadays, we witness a growing yet slow increase in the use of APDT in clinical treatment. Although a scanty number of existing clinical trials about PDT are performed on diseases other than periodontitis, but in the light of recent researches it is plausible to hope that this method can be applied to other infectious diseases as well.

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