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Photodynamic therapy as alternative therapy for prostate cancer and colorectal carcinoma as well as an antimicrobial treatment – a systematic review

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ABSTRACT

INTRODUCTION: Photodynamic therapy (PDT) is used in many different oncologic fields. This study includes PDT in prostate cancer (the second most common neoplasm after lung cancer in men in the European Union), colorectal cancer (third in men, second in women after breast cancer,) as well as a therapy for infectious problems accompanying these oncologic diseases. This review aims to give a general overview of the PDT application to those diseases in the field of clinical trials to emphasize its curative, and insufficiently exploited potential.

MATERIAL AND METHODS: Literature on PDT for cancer treatment with the following medical subject headings search terms: colorectal cancer, prostate cancer , photodynamic therapy, clinical trials, antimicrobial photodynamic therapy and bacterial infection was reviewed. The articles were selected by their relevance to the topic.

RESULTS: There are many positive and promising trial results from I to II/III phase for the use of PDT in colorectal cancer both in less advanced tumors as well as in the palliative therapy of advanced lesions. As well in prostatic cancer some studies had evaluated a negative biopsy rate after PDT. The most common adverse events were haematuria, erectile dysfunction, and dysuria. It also has been proven that PDT can be used as an adjuvant for the treatment of infectious diseases. The use of photosensitizer methylene blue, toluidine blue O (TBO), indocyanine green with light diode laser centered at (630±10 nm) and (650±10 nm) wavelengths have been shown to have significant results for the treatment of infectious diseases because of bactericidal properties. In the skin diseases, a PDT has been tested with promising results in different infections. Therefore, it is presented as a possible treatment option against antibiotic resistant microbes.

CONCLUDING REMARKS: PDT seems to be a safe and a feasible treatment option for colorectal cancer. Theoretical assumptions confirmed by many results of preclinical studies taking into consideration an increasing number of analyzed clinical trials, should lead to the development of optimized standards by using PDT in colorectal cancer treatment.

Review results show that PDT for patients with prostate cancer can be considered as effective based on single-arm clinical trials. Meanwhile, this study reveals that there are not only low levels of side effect rates but also insignificant effect on both urinary and erectile function.

These findings also suggest that a PDT can be an efficient method in the treatment of localized and superficial infections.

INTRODUCTION

Prostate cancer is a major cause of disease and mortality among men, and each year 1.6 million men are diagnosed with and 366,000 men die of prostate cancer (Siegel et al. 2017). Current treatment options for men with localized PC include active surveillance and radical therapy. The optimal treatment should provide cancer control with only few side effects (Kasivisvanathan et al. 2013). Radical prostatectomy is the first-line therapy for patients with prostate cancer. However, considering the morbidity and prognosis, the risks and efficacy of radical therapy were frequently not identified (Kawczyk-Krupka et al. 2015).Photodynamic therapy (PDT) is one of the focal therapies used for prostate cancer. This treatment modality uses laser of a specific wavelength in the presence of oxygen to activate a photosensitizing medication. This process causes localized cell death or tissue necrosis (Zhu et al. 2005). PDT has been used for neoplasms including cancers of lung, head and neck, pancreas, esophagus, and bladder (Gheewala et al. 2017). Since the 1990s, studies of PDT for localized PC have been reported (Windahl et al.1990).

Colorectal cancer is the third most commonly diagnosed cancer and fourth leading cause of cancer-related deaths, it accounts for almost 10% of cancer-related deaths in Western countries. This cancer is associated with a high risk of metastasis and recurrence despite an increased availability of diagnostic and therapeutic strategies. To treat patients with colorectal cancer, an approach that selectively targets cancer cells without damaging normal cells and which minimizes the risk of perforating the intestinal barrier is needed (Kawczyk-Krupka et al. 2015). Early detection of precan-cerous polyps may prevent the onset of colorectal neoplasm or increase the chances of a successful treatment. Currently, several different screening tests are available including endoscopy, stool-based blood tests, and radiology-

based tests. Colorectal cancer is commonly treated by tumor resection, as chemotherapy and radiation have proven to be less effective, especially if the tumor has metastasized. Resistance to therapies occurs in almost all patients with colorectal cancer, especially in those with metastatic tumors. Cancer stem cells have the ability to self-renew, and their slow rate of cycling enhances resistance to treatment and risk of tumor recurrence. Most metastatic tumors are unable to be surgically removed, thus creating a need for treatment moda-lities that target cancers directly and can destroy cancer stem cells. Photodynamic therapy involves a photosensitizer that when exposed to a light source of a particular wavelength becomes excited and produces a form of oxygen that kills cancer cells. Photodynamic therapy is currently being investigated as a treatment modality for colorectal cancer, and new studies are exploring enhancing photodynamic therapy efficacy with the aid of drug carriers and immune conjugates. These modifications could prove effective in targeting cancer stem cells that are thought to be resistant to photodynamic therapy. In order for photodynamic therapy to be an effective treatment in colorectal cancer, it requires treatment of both primary tumors and the metastatic secondary disease that is caused by colon cancer stem cells. This review focuses on current photodynamic therapy treatments available for colorectal cancer and highlights proposed actively targeted photosynthetic drug uptake mechanisms specifically mediated towards colon cancer stem cells, as well as identify the gaps in research which need to be investigated in order to develop a combinative targeted photodynamic therapy regime that can effectively control colorectal cancer primary and metastatic tumor growth by eliminating colon cancer stem cells.

PDT is considered as a complementary therapy aimed at preventing tumor recurrence after surgical resection of colorectal cancer (Shishkova et al. 2013) making a suitable approach for continuous removal of small fractions of tumors (Barr et al.1990). It has also been reported that PDT is an effective alternative treatment for drug-resistant colorectal cancer (Halaburková et al. 2017). PDT uses a modality-based photo-sensitizer, which selectively affects cancer cells, using excitation and light-absorption in the presence of oxygen to produce a high con-centration of reactive oxygen species (ROS), such as singlet oxygen and other free radicals (Kwiatkowski et al. 2018). The resulting damage cannot be overcome by the antioxidant system to protect the cell from oxidative damage, leading to necrosis, apoptosis, or autophagy of the target cell and tissue (Broekgaarden et al. 2015).

The broad antibiotic resistance of hospital pathogens is inducing human morbidity and mortality, as well as hospital costs (Geralde et al. 2017). The antibiotic resistant strains of bacteria imply the demand for alternative treatments for infectious disease. One strategy that may lead to improved antimicrobial treat-ment is the application of anti-microbial photo-dynamic therapy (aPDT) (Nakonechny et al. 2010). a PDT involves the use of a chemical photosensitizer or a nontoxic photoactivatable dye, visible light, and reactive oxygen. The therapy is based on the energy (absorbed as light via the intracellular photosensitizer) trans-ferred to the oxygen molecules producing extremely reactive mediation, such as singlet oxygen and superoxide, that are noxious to the cells(Mahmoudi et al. 2018). The spread of multi-resistant bacterial strains is one of the most worrying threats to public health in recent years and has arisen due to the excessive use of antibiotics (Fotinos et al. 2008). In view of the prediction of the "end of the antibiotic era" (Nordmann et al. 2011), antimicrobial photo-dynamic therapy is starting to be considered as a promising alternative approach to resistant infections and has the further advantage of not leading to the selection of resistant strains (Sperandio et al. 2013).Antimicrobial PDT is particularly good for dental (Sprendido et al. 2013, Dai et al., 2009) and dermatological (Choudhary et al. 2009) applications, involving the light irradiation of a tissue containing microorganisms that were previously exposed to a photosensitizing dye (PS). This PS should be able to generate reactive oxygen species (ROS) in the presence of light and oxygen (Kawczyk-Krupa et al. 2015). In order to be suitable for antimicrobial PDT, the ideal PS should possess low levels of dark toxicity and the presence of absorption bands in the so-called optical window (600-900 nm) for sufficient tissue penetration of light (Sharma et al. 2011). The PS should have a high yield of excited electronic triplet state and of singlet oxygen (Sharma et al. 2011). The PS should be excited by visible light of the correct wavelength

(wavelength absorbed by the PS) to enter a long-lived triplet state. This particular state of the PS can then interact with molecular oxygen by energy transfer or by electron transfer processes. (Castano et al. 2004). After being excited to the short-lived singlet state the PS can lose energy by fluorescence, heat conversion or can undergo intersystem crossing to the long-lived triplet state. In case the PS is a fullerene, energy loss by fluorescence is negligible, and in the absence of oxygen fullerene triplet states lose energy by phosphorescence (Sharma et al. 2011). mAntimicrobial PS should be able to kill multiple classes of microbial cells at relatively low concentrations and low fluences of light. The PS should also be reasonably nontoxic in the dark and should show selectivity for microbial cells over host mammalian cells. In fact, the microbial uptake process of PS with cationic substituents such as quaternary ammonium groups is rapid when compared to the uptake of these PS by host mammalian cells, which slowly occurs over time (Soncin et al. 2002). Therefore, if light is delivered soon after applying the PS to the infected area, microbial cells can be killed without causing harm to the host tissue (Sperandio et al. 2013).

BACTERIA AND COLORECTAL CANCER

The growing evidence suggests that bacteria can play an important role in the initiation and progression of colorectal neoplasm by inducing chronic inflammation and by the release of carcinogenic metabolites (Marchesi et al. 2011). Some of the bacteria most commonly associated with colon cancer include: *Fuso-bacteium nucleatum* (Shang et al. 2018), *Bacteroides fragilis*, and *Escherichia coli* (Dejea et al. 2018). Inflammatory bowel disease (IBD)-associated colorectal cancer is a classic example of an inflam-mation-induced cancer (Choi et al,2017).

The intestinal tract acts as a reservoir for various microbial species, together known as the intestinal microbiota (Thursby et al. 2017). In the last two decades, strong evidence has indicated that the gut microbiota plays a critical role in providing nutrients to the gut mucosa, in the development of the mucosal immune system, and in preventing pathogen colonization (Kang et al. 2017). The mucosal immune system's main tasks are to mount an immune response against pathogenic microbes and to maintain tolerance against food and commensal microbial antigens. Loss of tolerance to commensal enteric microorganisms finally leads to uncontrolled chronic inflammation like that seen in patients with IBD. In addition, since the colon carries 10^{12} bacteria/mL, compared to 10^{2} bacteria/mL in the small intestine, the colon presents a 12-fold higher risk of developing tumors (Tjalsma et al. 2012). Recent findings suggest that microbes such as *F. nucleatum*, (Kostic et al. 2013) enterotoxigenic *B. fragilis*, *Streptococcus bovis*, *E. coli*, and *Klebsiella pneumoniae* can play an important role in colon cancer development (Antonic et al. 2013). These gut-associated bacteria can increase the risk of tumor malignancy by several mechanisms including secretion of mutagenetic metabolites and promoting inflammation. Lately, a link between gut bacteria and the efficacy of anti-PD-1 immunotherapy has also been uncovered (Routy et al. 2018). Collectively, these studies show important link between bacteria and colorectal cancer pathogenesis. Although several studies have demonstrated the involvement of micro-bes in IBD and cancer progression, the mechanistic insights into how these bacteria actually lead to these conditions or their potential role in relapse of disease are yet to be discovered.

URINARY MICROBIOME IN MEN WITH PROSTATE CANCER

Studies profiling the urinary microbiome in men with and without a biopsy proven diagnosis of prostate cancer revealed that the urinary microbiota of most men is predo-minated by a single genus and notably by species of *Coryne-bacterium*, *Staphylococcus* and S*treptococcus*. While similar trends have been reported in urine samples from women, female urine samples differ in that the predominant microorganisms are *Lactobacillus* and *Gardnerella* (Pearce et al. 2014, Shrestha et al. 2018). Interestingly we identified a subset of men with predominant urine representation from *Lacto-bacillus* or *Gardnerella* species. The presence *G. vaginalis* was associated with chronic inflammation in corresponding prostate biopsies. This raises the intriguing possibility that some men may harbor urinary microbiota associated with inflammatory conditions in women (eg bacterial vaginosis – BV).

Several additional species of pro-inflammatory bacteria and/or known uropathogens were differentially represented in men with prostate cancer. Notable examples included *A. schaalii*, an emerging uropathogen of potentially under-estimated clinical significance due to difficulty with phenotypic identification (Chu et al. 2009). *A. schaalii* was found in men with and without prostate cancer but this species was included in the cluster of pro-inflammatory bacteria more prevalent in men with cancer (Shrestha et al. 2018). As mentioned, species of Ureaplasma were also differentially abundant in the urinary microbiota of men with prostate cancer. In Shresta's study, the cancer on SB samples had the highest average number of OTUs and none showed a predominance of *Corynebacterium*, *Staphylococcus* or *Streptococcus* (Shrestha et al. 2018). There were several limitations to the current studies, including the fact that all men were being seen for some indication for prostate biopsy. Although men in the benign group were biopsy negative for prostate cancer, they nevertheless represented a population with elevated PSA and were likely to have BPH and/or prostatic inflammation. Indeed, the men in the benign group had a larger average prostate TRUS volume than the men with cancer or cancer on SB, indicating prostate enlargement in this group. As BPH is also associated with chronic inflammation, (Gandaglia et al. 2013, Shrestha et al. 2018) future studies warrant an association of urinary microbiota with the presence of BPH. In addition, it is likely that a fraction of the men with a negative biopsy actually had prostate cancer because the false-negative rate of TRUS guided prostate biopsy is commonly reported to be up to 30%. Future followup studies will necessitate a true control population of men without an indication for prostate cancer to determine whether the urinary microbiome profile is unique in those without prostate disease or rather consistent with the control group in the current study (Shrestha et al. 2018). Several studies have shown that there is an increased risk of prostate cancer in men with a history of prostatitis (Shrestha et al. 2018, Cheng et al. 2010).The key hypothesis that emerged from the current study is that pro-inflammatory species that reside in the urinary tract may serve as a potential source of inciting chronic inflammation in the prostate. Ultimately establishing the link between the urinary microbiome and chronic inflammation in the prostate may be keenly important in terms of developing strategies for prostate cancer prevention.

INTESTINAL MICROBIOME AND PROSTATE CANCER RELATIONSHIP

Prostate cancer is the second leading cause of death in the United States and accounts for 1 in 5 new diagnoses in the male population (Siegel et al. 2019). The lifetime risk for prostate cancer is about 16%, with 276,000 new cases in 2018 (The Global Cancer Observatory ,2018). In Europe, the statistics are similar (Sha et al. 2020). Standard treatment for prostate cancer include androgen-based therapies; however, this treatment does not change other risk factors for prostate cancer, such as bacterial infections, environmental stimuli, or inflammatory markers. Due to prostate cancer's high prevalence, these alternate risk factors are explored in recent years (Sha et al. 2020). With an increasing under-standing of microbial effects on carcinogenesis, studies have been conducted exploring specific GI microbes and prostate cancer outcomes. The composition of intestinal microbiome may influence the metabolism of certain compounds that may be associated with increased prostate cancer risk (Sha et al. 2020). Intake of calcium in dairy products (Lampe 2011), red meat (Punnen et al. 2011), and fat (Sonn et al. 2005) have been linked to increase prostate cancer risk or progression. This may relate to the micro-biome's role in phytochemical digestion (Musso et al. 2011), dairy product digestion (Masood et al. 2011), and the generation of inflammatory molecules (Sha et al. 2020, Arthur et al. 2012), which can influence neoplastic development, not only locally in gut mucosa but also in distant locations.

Antibiotics commonly used in hospital and outpatients environment lead to microbial selection, in most cases with adverse result. A reduced diversity profile can lead to an overgrowth of bacteria that promote inflam-mation and neoplasia. Studies have shown that antibiotic usage increases likelihood of bacterial infections from *Clostridioides difficile* and methicillin-resistant *Staphylococcus aureus* (Hunter et al. 2010). These bacterial species are typically present in the GI microbiome, but are able to proliferate under conditions of microbial disruption. The association between prostate cancer risk has been investigated in the context of antibiotic exposure. Antibiotic-induced

changes in microbiota form changes in intestinal permeability, introducing risk of neoplastic changes (Tulstrup et al. 2011). Another paper shows that an antibiotic would cause a change in the bacterial diversity of the GI and induce chronic inflammation. The risk of prostate cancer increased moderately with the use of penicillins, quinolones, sulphonamides, and tetracyclines (Boursi et al. 2015). When descry-bing how the micro-biome affects distant carcinogenesis from the GI, as in the case of prostate cancer, a functional estrobiome, or enteric bacterial genes that are able to meta-bolize estrogen were postulated (Plottel et al. 2011). β-Glucuronidases and β-glucuronides are particularly important in the metabolism of estrogen by conjugation and deconjugation. Elevated estrogen levels were reported in patients with prostate cancer compared to healthy con-trols (Althuis et al. 2004). Estrogen promotes carcinogenesis by activating polycyclic aromatic hydrocarbons (PAHs) which involve the forma-tion of carcinogenic metabolites, diol epoxides and radical cations. Diol epoxides and radical cations react with DNA that can lead to cancer-promoting mutations. This estrogen mechanism is linked to Plottel's hypothesis of the estrobiome, or estrogen-metabolizing bacteria, and therefore when disturbed would cause an increase in serum estrogen (Plottel et al. 2011).

In addition to the estrogen-driven carcino-genesis hypothesis, chronic inflammation has been described to create dysbiosis and subse-quently increase cancer risk. *In vivo* studies showed that GI tract bacterial infection is sufficient to enhance prostate intraepithelial neoplasia (PIN) and microinvasive carcinoma (Poutahidis et al. 2013). Induction of neoplasia was started by the prior neutralization of inflam-matory molecules such as tumor necrosis factor α, suggesting that GI microbial-based inflam-mation plays a large role in tumor formation and progression. There are certain microbes that increase the risk of prostate cancer *in vivo*. *Campylobacter jejuni* was found to induce cell cycle arrest, chromatin fragmentation, and cell death from its toxin termed cytolethal distending toxin (Lara-Tejero et al. 2000). Clostridium was found to convert gluco-corticoids in the gut to androgens by side-chain cleavage, which could contribute to prostate cancer development (Ridlon et al. 2013). *Escherichia coli* is common in the human gut and is typically in symbiosis with the host; however, it was (Cuevas-Ramos et al. 2010) noted that *in vivo* infection of *E. coli* induced DNA damage response with signs of incomplete DNA repair. In addition, *E. coli* has been found to be associated with prostate inflammation. Mice infected with *E. coli* developed bacterial prostatitis and many deve-loped dysplastic changes; zero of the control mice developed prostate infections or inflam-mation (Elkahwaji et al. 2009).

There were studies on rectal swabs from men (rectal microbiome profiles were sequenced prior to transrectal prostate biopsy). There were significant increases in proinflammatory *Bacte-roides* and *Streptococcus* species in those diagnosed with prostate cancer (Sha et al. 2020). Inflammation may be related to neoplasia by inflicting cellular and genomic damage, trig-gering a cascade of cell repair, angiogenesis, and tissue repair on a larger level (Nakai et al. 2013). Furthermore, it has been hypo-thesized that reactive oxygen species and reactive nitrogen species are released through immune cells during times of inflammation, directly damaging cells and DNAs (De Marzo et al. 2007). This oxidative damage and cellular death is the cause of proli-ferative inflammatory atrophy, which is identified as a precursor to prostatic neoplasia and potentially adeno-carcinoma (De Marzo et al.1999).

The studies exploring the specific micro-organism and prostate cancer risk discussed above are summarized in table1 (Sha et al. 2020)

FOLIC ACID/PROBIOTIC THERAPY

What is more there were several research programmes about microbiota, folic acid meta-bolism and prostate cancer. High dietary folate intake was associated with a decre-ased risk of prostate cancer. Microbiota involved in folate production were increased in men without prostate cancer; therefore, there seems to be a difference between endo-genous folate produc-tion and folate supplementation (Liss et al. 2018). This could have implications for preven-tative medicine by encouraging men to use probiotics for natural folate production and discourage use of folate supplements.

Table 1. Studies discussed about specific gastrointestinal microbiota and prostate cancer

Study	Results	Bacteria involved
Liss et al. (2018)	Rectal swabs were taken and found an increase in *Bacteroides* and *Streptococcus* in those with prostate cancer compared to controls.	*Bacteroides, Streptococcus*
Alanee et al. (2019)	*Bacteroides* from fecal samples was highly associated with prostate cancer diagnosis.	*Bacteroides*
Golombos et al. (2018)	*Bacteroides massiliensis* was in higher relative abundance in prostate cancer cases, while *Faecalibacterium prausnitzii* and *Eubacterium rectalie* was in higher relative abundance in controls.	*B. massiliensis, F. prausnitzii, E. rectalie*
Miyake et al. (2019)	Men with more extensive prostate cancer disease (T2c-3b) had a higher rate of *Mycoplasma genitalium* infection compared to those who had benign prostate hyperplasia.	*M. genitalium*

HISTORY OF PHOTODYNAMIC THERAPY

The origin of the laser/light therapy found as an alternative treatment in medicine from ancient to contemporary time. Phototherapy trace its root back to ancient Greece, Egypt and India, however not applied for centuries (Mahmoudi et al. 2018). Ultimately, it has been rediscovered for the westen society at the outset of the 20th century by a Danish physicist, Niels Finsen. He successfully used photodynamic therapy by applying heat and light filtered through a carbon lamp for the treatment of cutaneous tubercles known as lupus vulgaris (Daniell et al.1991). The idea of necrobiosis caused by action and reaction between light and chemicals were the earliest described by Raab in Munich. He found that chemical changes in the presence of a pigment called acridine light, inducing the death of a paramecium (Raab et al.1990). Photodynamic therapy was confirmed by the Food and Drug Administration in 1999 to treat pre-cancerous skin lesions in the head and face (Lui et al.1992).

THE MECHANISM OF ACTION OF PHOTODYNAMIC THERAPY

PDT method binds the application of visible light, combined with a photosensitizer (PS) and with the oxygen (Mahmoudi et al. 2018). PDT is based on the interaction of visible light and a photosensitizer agent which under photo-activation generate short lasting cytotoxic radicals locally. After stimulation, the photosensitizer is converted from singlet to triplet state by an intersystem crossing process which, in turn, reacts with surrounding molecules to produce radical species and hydrogen peroxide, or transfers its energy to molecular oxygen to manufacture singlet oxygen. Oxygen species that are capable of eliminating target cells by oxidative stress to cell membranes and other cellular parts (Darabpour et al. 2016).

Photodynamic therapy involves the generation of ROS resulting from the interaction of photosensitizer and VIS light. However, VIS light is too weak to penetrate deep into the tissue. Also, ROS production is limited due to the hypoxic environment of tumor and the colon tissue. Furthermore, ROS production consumes most of the oxygen available to an induced hypoxic environment in the tissue, which further potentiates tumorigenesis. Talaporifin sodium (TS), a light-activated drug/photo-sensitizer, has been approved in Japan for the treatment of early-state endobronchial cancer (Wang et al. 2010). Activation of TS with a 664 nm VIS range light generates a single oxygen species, resulting in the induction of apoptotic cell death. In a Phase II trial of TS in patients with colorectal cancer and metastasis to the liver, the efficacy of the treatment depended on the number of excitation sources used to activate the drug (Kujundžić et al. 2007). This study shows that the treatment efficacy depends on the penetration of cancer tissue by the excitation light with enough photons to activate the photo-sensitizer. UCNPs with emission at UV range could be used to overcome these limitations associated with VIS light and ROS production. Deep penetrating NIR light can be used to excite the UCNPs, and the localized emission of UV can be used to kill the surrounding carcinogenic cells.

PHOTOSENSITIZERS

An optimal photosensitizer ought to have favorable structural features including physical, chemical, and biological characteristics. Many optical photosensitizers for photodynamic therapy have been tested both in vitro and in vivo. PDT photosensitizers are found in this chemical groups: porphyrins (5-aminolevulinic acid is a porphyrin precursor), chlorine and dyes such as toluidine blue O (TBO), methylene blue (MB) and Azure.

PHOTOSENSITIZERS WITH CATIONIC CHARGES

It is well known that Gram-positive bacteria can be inactivated with PDT (Sperandio et al. 2013); however Gram-negative bacteria are far more resistant to this therapy (Malik et al.1992). To overcome this limitation, besides penetrability the outer membrane with PMBN (Nitzan et al.1992) or Tris/EDTA (Bertoloni et al.1990) to allow non-cationic PS to be used, some cationic PS may also be employed.

Polycationic colours need to gain access through the outer membrane to more sensitive parts of the cell (Hamblin et al. 2002); however, the efficacy of this process depends on the size of the polycationic chain . Conjugates with eight, thirty-seven lysines and free ce6 can efficiently inactivate *Staphylococcus aureus*; but only the conjugate with thirty-seven lysines could kill *E. coli*. It is plausible that 37-lysine can interact with the outer membrane of *E. coli*, perhaps causing the loss of some LPS and rendering the remaining LPS more permeable, allowing the conjugate to penetrate. On the other hand, the 8-lysine conjugate did not provoke the same effect, which was probably due to its insufficient polycationic character (Hamblin et al. 2002).

NOVEL PHOTOSENSITIZERS FOR ANTIMICROBIAL PDT OF GRAM-NEGATIVE BACTERIA

One of the most studied groups of PS consists of porphyrin derivatives, which are described in inventions and may act as photodynamic agents, since these derivatives generate reactive oxygen forms such as singlet oxygen or oxygen free radicals when irradiated with appropriate wavelengths and in the presence of oxygen. Consequently, these compositions are suitable for curative or prophylactic treatment of several medical conditions including infections with Gram-negative cocci (e.g *Neisseria* sp.) and Gram-negative bacilli (e.g *E. coli*) (Love et al. 2011).

Another family of potent photosensitizers are the halogenated xanthenes, since they also become photoactivated upon shining visible light on the treatment site that was previously exposed to these compounds (Dees et al., 2005). These medicaments are in turn suitable for intracorporeal administration and thus were employed to achieve photodynamic therapy in human or animal tissues. In three distinct inventions, the primary component of given medicaments is a halogenated xanthene or a halogenated xanthene derivative. Furthermore, this xanthene molecule is more preferably Rose Bengal or a functional derivative of Rose Bengal (Dees et al. 2011). As it was explained before, the susceptibility of bacteria to phenothiazinium mediated PDT depends on whether the bacteria are Gram-positive or Gram-negative. New methylene blue and di methyl methylene blue, for example, were proven to be efficient at inactivating MRSA (Wainwright et al.1998). Biologically active methylene blue derivatives are also effective in deactivating a wide range of microorganisms, including Gram-positive and Gram-negative bacteria, MRSA and fungal infections (Brown et al. 2011).

On the other hand, naturally occurring and synthetically available siderophore structures can be conjugated chemically with photoactive compounds such as chlorin to improve their penetration into bacterial cells, via microbial proteins that recognize and transport iron-loaded siderophores. In that way, PS that otherwise could not cross the cell wall and membranes can then be transported inside the bacteria (Grafe et al. 2004) allowing Gram-negative bacteria to be susceptible to this particular approach. Actually, the siderophore-transporting systems of microbes are specific to individual classes of bacteria and fungi. Due to that, siderophore-conjugates with PS are not taken up by mammalian cells, what makes them a good alternative for antimicrobial PDT, since they are not harmful to the host and are truly specific for pathogenic microbes. Then, the application of this method presents a highly efficient treatment of pathogenic Gram-positive and Gram-negative bacteria such as *P. aeruginosa*, *E. coli*, *Strepto-coccus pyogenes*, *S. aureus,* as well as for other antibiotic resistant microbial infections including infections that

occur in chronic wounds (Sperandio et al. 2013, Grafe et al. 2004).

Another patent describes a method and composition that utilizes Safranin O in conjunction with light irradiation (530 nm) in order to destroy microbes, especially bacteria. The Safranin O containing compound must be introduced to the treatment area and then, after a sufficient period of time, the light must be delivered to this area. This is an effective PDI approach for Gram-positive and Gram-negative bacteria, particularly good for areas surrounded by complex media such as blood serum, blood or saliva (Albrecht et al., 2005). In another study *E. coli* was only sensitive to porphyrin and light after suffering a pretreatment with toluene, which then induced susceptibility of this Gram-negative bacteria to PDT with hematoporphyrin derivative (Boye et al.,1980). In addition, positively charged (cationic) PS, including porphyrins and pthalocyanines, promote efficient inactivation of Gram-negative bacteria without the need of modifying the natural structure of the cellular envelope (Minnock et al.,1994, Merchat et al.,1996). Finally, not all microbial infections are suitable for PDT, because some infection sites may not be accessible to light (Love et al., 2007).

Several improvements are continuously made in PDT. tThe method with PS selected from toluidine blue O, methylene blue, dimethylene blue or azure blue chloride that can be employed to both hard and soft tissues was studied. Even military medical procedures are mentioned in the text, illustrating a particular utility for this therapy (Clements et al., 2010).

Hydrophilic cationic and anionic photosensitizers have been found to inactivate pathogenic bacteria. In a recent invention photosensitizers are formulated in calcium phosphate nanoparticles formulations for antibacterial PDT. These formulations were tested against *S. aureus* and Gram-negative *P. aeruginosa* demonstrating a very high percentage of killing (Gitter et al., 2011).

It has been said that certain edible or ingestible food colours are equal to or even superior to synthetic chemical photodynamic agents. They are of non-toxic nature, which definitely configures an advantage. In addition, they have the ability to be safely consumed and their breakdown is always to safe and environmental friendly products (Olson et al., 2010). By that means, an invention teaches how to treat an infected animal or decontaminate a surface, for example, by using a safe natural or synthetic food coloring agent that has photodynamic properties (Olson et al. 2010, Sperandio et al., 2013). The PS may be selected from the group of chlorophylls, carotenoids, flavenoids, quinonoids, coumarins, indigoids, curcuminoids, befalins, acthocyanins, cyanines, indocyanines, phthalocyanines, rhodamines, phenoxazines, phenothiazines, phenoselenazines, fluoresceins, porphyrins, benzoporphyrins, squaraines, corrins, croconiums, azo compounds, methine dyes, and indolenium (Sperandio et al., 2013). A novel series of PS that have advantages over other known compounds has been described. These compounds are actually meso-substituted porphyrins that have an absorption in the region of the visible spectrum, high molar extinction coefficients, and high quantum yield in singlet oxygen production (Roncucci et al., 2011). As previously mentioned, there are some limitations of porphyrin-based PDT. Among the limitations is the poor selectivity toward eukaryotic cells and the micoorganisms. In tumors, this selectivity can be enhanced by increasing the degree of hydrophobicity of the PS or by imparting amphiphilic properties to its molecule (Jori et al., 1996). Alternatively, these meso-substituted porphyrins are conjugated with a bio-organic carrier, ensuring high efficiency and selectivity against the target, i.e. Gram-negative bacteria (Roncucci et al., 2011).

BLUE LIGHT ANTIMICROBIAL PHOTOINACTIVATION

The advantages of using blue light alone to kill resistant microbes, is that the light is not as harmful to the host tissue or to the surroundings compared to UV light and moreover no added exogenous PS or dye is required (Dai et al., 2012). The most effective range is from ~390 nm to 420 nm (more accurately termed "violet" light), the next most effective range is from 450-480 nm and possible the least effective range is from 420-450 nm. Over the last five years a wide range of microbial cells, including Gram-positive bacteria, Gram-negative bacteria, mycobacteria, molds, yeasts and dermatophytes have been shown to be susceptible to blue light (Wang et al., 2017). Studies have been carried out *in vitro* using planktonic cells or biofilms, *ex vivo*, and *in vivo* using animal models (preclinical) and even in patients (clinical trials). The biological response to blue-light was firstly reported in 1881 by Charles Darwin when he

described a blue light induced phototropic response in plants (Darwin, 1881). Blue light can regulate bacterial motility, suppress biofilm formation, and subsequently potentiate light inactivation of bacteria. On the other hand, the presence of blue light may also activate or increase bacterial virulence (Hamblin et al., 2019).

The lethality of blue light for bacteria has been reported both *in vitro* and *in vivo*. Blue light can mediate a broad-spectrum antimicrobial effect on both Gram-negative and Gram-positive bacteria. While the wavelength range of 390-420 nm has been reported to be the most effective antimicrobial spectral range, both 455 nm and 470 nm have also been found to have some antimicrobial effects on some bacterial species (e.g., *S. aureus*). The mechanism of the antimicrobial effect of blue light is that blue light excites endogenous intracellular metal-free porphyrins to behave as PS as described above for the case of aPDI. This photon absorption then leads to energy transfer from the porphyrin triplet state to oxygen producing $^1O_2$ in a similar manner to PDT (Hamblin et al., 2019, Hamblin et al., 2005). Different bacteria demonstrate variable susceptibilities to blue light. Studies have reported that Gram-positive species, in general, were more susceptible to 405 nm light inactivation than Gram-negative species, which is generally consistent with the results obtained in a recent study (Murdoch et al., 2013). It has also been theorized that the differences in inactivation kinetics may be due to organism-specific differences in porphyrin levels, different individual porphyrin sub-types, or different porphyrin subcellular localizations (Maclean et al., 2009). Moreover, it has been speculated that less oxygen-tolerant bacterial species may be particularly susceptible to the effects of ROS as some microaerophilic species have been found to possess fewer key antioxidant defenses than most aerobes (Jean et al., 2004). Some studies have shown blue light to be capable of inactivating the anaerobic oral pathogens *Prevotella, Porphyromonas*, and *Fusobacterium, P. acnes* as well as microaerophilic pathogen as and *H. pylori* (Feuerstein et al., 2005).

Table 2. Studies about blue light antimicrobial action

Light Source	Radiant exposure	Bacterial species/strains	Inactivation efficacy	Ref
405-nm diode laser	20 J/cm^2	*H. pylori*	>99.9%	Hamblin et al. [2005]
380-520 nm broadband light	4 . 2-42 J/cm^2	*P. gingivalis, P. intermedia, P. nigrescens, P. melaninogenica, S. constellatus*	*P. intermedia* and *P. nigrescens*: >5 log10 at 4 . 2 J/cm^2; *P. melaninogenica*: >5 log10 at 21 J/cm^2; *P. gingivalis*:1.83 log10 at 42 J/cm^2	Soukos et al. [1998]
405 and 470 nm light	15 J/cm^2	*S. aureus, P. aeruginosa*	*S. aureus*: 90% at 405 nm, 62% at 470 nm; *P. aeruginosa*: 95.1% at 405 nm, 96.5% at 470 nm	Guffey and Wilborn
407-420 nm	75J/cm^2	*P. acnes*	less than 2-log10 units (99%) illuminated once; decreased by 4-log10 units (99.99%) after two illuminations and by 5-log10 units (99.999%) after three illuminations	Feuerstein et al. [2005]
405-425nm LED	110 J/cm2	*A. baumannii*	7.64-log10 CFU	Dai et al. [2011]
	118-2214 J/cm^2	*S. aureus, S. epidermidis, E. faecalis, S. pneumoniae, Corynebacterium striatum, E. coli, K. pneumoniae, P. aeruginosa, Serratia marcescens C. albicans.*	Complete inactivation (> 4-log10 CFU) in suspension was achieved in all of the isolates tested.	Dai and Gupta [2012]

MATERIAL AND METHODS

Literature on PDT for cancer treatment with the following medical subject headings search terms: colorectal cancer, prostate cancer, photodynamic therapy, clinical trials, antimicrobial photodynamic therapy and bacterial infection was reviewed. The articles were selected by their relevance to the topic.

RESULTS

PDT AND PROSTATE CANCER

As the most common treatment alternatives for localized prostate cancer, radical surgery and radiotherapy are used with a considerable morbidity. Patients with low risk and localized PC do not benefit from radical prostatectomy (Wang et al., 2019, Nelson et al., 2014). A number of alternative (focal) treatments such as high-intensity focused ultrasound, cryotherapy, and radiofrequency have been used (Gheewala et al., 2017, Golan et al, 2017). Although cancerous cells are destroyed, traditional focal treatment frequently leaves the tumor vessels intact, which can lead to recurrence of the tumor while treatment is insufficient, leaving not only the tumor parenchyma but also tumor vessels. PDT is specialized in target ablating and can prevents recurrence by reactive oxygen species such as singlet oxygen and free radicals (Wang et al., 2019, Dolmans et al., 2003). Percent negative biopsy, Gleason score, clinical stages, and PSA are tools for risk estimation in prostate cancer. Unlike radical prostatectomy and radiotherapy, it is suitable for a biopsy-based outcome after PDT (Nelson et al., 2014, Azzouzi et al., 2017).

The most important finding in recent studies was that the pooled rate of negative biopsy after PDT and decreased PSA were 55.0% and 35.0%, respectively. The control group in some studies was active surveillance and several other focal treatments (such as cryotherapy and brachytherapy), respectively (Azzouzi et al. 2017). According to the result of the randomized clinical trials, negative biopsy rate of active surveillance was less than one-third of the rate in the PDT group (Wang et al. 2019, Azzouzi et al., 2017). All the patients of the studies in this systematic review were considered having low-risk, localized PC which was well or moderately differentiated (most biopsy Gleason score was less than 6). The PSA after PDT was less than 4.0 ng/mL in the follow-up duration. In the study of high-risk PC (Nathan et al. 2002), although the PSA decreasing rate was 42.0%, the PSA after PDT was still higher than 10.0 ng/mL. This suggested that PDT was not suitable for the patients with high-risk, poorly differentiated PC. On the other hand, PDT can play an important role in patients who have recurrence after radical prostatectomy or who have failed previous definitive radiotherapy (Du et al. 2006).

The review studies show that rates of adverse events were variable but at a low level. By comparing PDT with cryotherapy, brachytherapy, and high-intensity focused ultra-sound, PDT appears to have a reasonably low rate of side effects (Wang et al. 2019), Barret et al. 2013). The most common adverse events were hematuria, erectile dysfun-ction, and dysuria. Due to the vascular target toxicity, hematuria always emerges in the duration of early posttreatment in about seven days (Kulik et al. 2014). Another notable complication was retention. There are_studies that found that retention was the most common serious adverse event in patients who underwent PDT. They thought it was associated with timing of withdrawal of the urinary catheter (Azzouzi et al. 2017). Other rare adverse events such as rectourethral fistulae and injury of seminal vesicle were almost asymptomatic and with a self-healing process, probably for extraprostatic sliding of an optical fiber (Wang et al. 2019). It is worth noting that photo toxicity is an inherent risk when using a photosensitizer (Kawczyk-Krupka et al. 2015).

The expected survival benefit of treatment for PC must be balanced against the related side effects such as erectile dysfunction and dysuria (Sachdeva 2015). Some studies found that occurrence of erectile dysfunction and incontinence during high-intensity focused ultrasound and cryotherapy was not only variable but also high (20.0-55.0%, 0.0-10.0%, 15.0-40.0%, and 1.0-10.0%, respectively)(Gómez-Veiga et al. 2014). In comparison to high-intensity focused ultrasound and cryotherapy, PDT has less effect on urinary and erectile function (Gómez-Veiga et al. 2014).Efficacy and functional outcomes of PDT were variable when using different photosensitizers. Padeliporfin and motexafin lutetium

were usually used in PC, whereas temoporfin was usually used in lung and head and neck malignancies (Dąbrowski and Arnaut, 2015). The selection of photosensitizer is important for patients if PDT is planned. Decreasing PSA was also associated with the follow-up duration. It indicated that a long-time follow-up is necessary when evaluating the changing PSA.

Table 3 PDT in prostate cancer-studies

References	PDT parameters	photosensilizer	patients	effect
Azzouzi et al (2017)	753 nm 150 mW/cm for 22 min 15 s	Padeliporfin	low-risk, localised prostate cancer (Gleason pattern 3) patiens, no previous treatment	safe, effective treatment for low-risk, localised prostate cancer
Barret et al (2013)	753 nm 150 mW/cm	Padeliporfin	Gleason 6	effective
Du at al (2006)		motexafin lutetium	Prostate adenocarcinoma	safe
Kasivisvanathan et al (2013)	753 nm 200/300 J/cm	TOOKAD	Gleason 3+3	effective
Kawczyk-Krupka et al (2015)	753 nm 150 mW/cm	palladium-based WST-09 and WST-11 photosensitisers	Prostate adenocarcinoma cells	effective

PDT AND COLORECTAL CANCERS

Recent studies have shown that photodynamic therapy (PDT) treatment has the ability to activate the tumor-specific immune responses by producing tumor-associated antigens from tumor cell residues, which afterward may be processed by APCs such as DCs and then presented to T cells (Gerosa et al. 2002). It is known that the immuno-logical memory response, which is the hallmark feature of adaptive immunities, plays crucial roles in protecting organisms from the second attack of pathogens including tumor cells (Ferlazzo et al. 2002). Upon a second encounter with the same pathogens, memory T cells can rapidly respond and mount faster and stronger immune responses than the first time the immune system response (Degli-Espsosti and Smyth, 2005). It is generally recognized that the underlying mecha-nisms of the combination therapy with ideal inhibition activities on the growth of both primary and distant tumors, as well as the immune memory protection to prevent tumor relapse, may be explained as follows.

The PDT destruction of primary tumors would generate a pool of tumor-associated antigens – TAA to trigger specific immune responses, which were then amplified by UCNP-Ce6-R837 - based PDT as the immune adjuvant, which combined with T-lymphocyte-associated protein 4 (CTLA-4) blockade would effectively induce the generation of TEM-based immune memory response to prevent tumor relapse, similar to the functions of cancer vaccines. More signify-cantly, PDT with UCNP-Ce6-R837 in combi-nation with the CTLA-4 checkpoint blockade not only showed excellent efficacy in eliminating tumors exposed to the NIR laser but also resulted in strong antitumor immunities to inhibit the growth of distant tumors left behind after PDT treatment. Furthermore, such a cancer immunotherapy strategy has a long-term immune memory function to protect treated mice from tumor cell challenge (Hayakawa and Smyth, 2006). This study presents an immune-stimu-lating UCNP-based PDT strategy in combination with CTLA-4 checkpoint blockade to effecti-vely destroy primary tumors under light exposure, to inhibit distant tumors that can hardly be reached by light, and to prevent tumor reoccurrence via the immune memory effect.

In summary, study demonstrates the great potency of integrating UCNP-based PDT with cancer immunotherapy to realize a remarkable synergistic therapeutic outcome in eliminating primary tumors, inhibiting distant tumors, and preventing tumor relapse. While immuno-therapy has become a highly promising paradigm for cancer treatment in recent years, it has long been recognized that PDT has the ability to trigger antitumor immune responses. However, conventional PDT triggered by visible light has limited penetration depth, and its generated immune responses may not be robust enough to eliminate tumors (Gang et al. 2018).

PHOTODYNAMIC THERAPY AN EMERGING TREATMENT MODALITY IN ONCOLOGY

Photodynamic therapy (PDT) is a promising method used for the control of a variety of cancers (Hu et al. 2014). PDT is a harmonized process which first requires the exposure of the cancer tissue to a photosensitizer (PS), administered either topically or intravenously, depending on the location of the targeted tissues (Portilho et al. 2013). A PS is a molecule that is taken up and localizes in the target cell and/or tissue and can only be activated by light (Wan and Lin,2014). Activation of a PS is achieved through exposure to laser irradiation at a specific wavelength. Once photons are absorbed by a PS, it is excited and stimulated from the ground state to a higher level of energy, a singlet state (Chiaviello et al. 2011). Alternatively, the molecule may convert to the triplet state through a mechanism called intersystem crossing, which results in a change in the spin of an electron. In this triplet state, the PS reacts with molecular oxygen and gives rise to free ROS that can destroy cancer tissue (Mroz et al. 2011). A major advantage of using PDT is that it achieves selective cell destruction and minimizes damage to adjacent healthy structures. PSs are taken up by all cells; however, they tend to preferentially localize in diseased tissue and remain in diseased tissue for a longer period of time due to the enhanced permeability retention (EPR) effect (Yo and Haa,2012). Consequently, it is vital to ensure PS activation only occurs once the proportion of PS in diseased tissue is greater than that present in healthy tissue (Josefsen et al. 2012). Other advantages of PDT over conventional treatment options include being a minimally invasive technique, lowering morbidity rate, ability to reserve the anatomic and functional integrity of many cells, minimal side effects, selective targeting, and no drug resistance, as well as reduced toxicity which allows for repeated treatment (Olivo et al. 2010).

SUBCELLULAR LOCALIZATION OF PHOTOSENSITIZERS (PS)

PS uptake and localization play a critical role in the effectiveness of PDT in the treatment of cancer. Subcellular localization of photosensitizers in different cellular components may induce various pathways of cell death/damage. Subcellular localization sites of PSs include the plasma membrane, lysosomes, Golgi apparatus, the nucleus and the mitochondria (Kim et al., 2014). PSs that accumulate in smaller amounts in more than one organelle (co-localization) may be used in combination to enhance the PDT efficacy of the PSs (Castano et al. 2004).

PS SOLUBILITY

Solubility also plays a role as most PSs are hydrophobic (Kim et al. 2014). Hydro-phobicity and a tendency to aggregate in aqueous environments hinder bioavailability of several PSs. Aggregation reduces increased uptake of photosensitization by the mononuclear phagocytic system (MPS) and decreased uptake by target cells as well as an increased risk of anaphylactic reactions (Sobczyński et al. 2013). Conjugation to nanoparticles can tune the water solubility and aggregation of the PCSs, without significantly affecting its photophysical properties (Chernonosov et al. 2014).

PS DELIVERY AND SELECTIVITY

Abundant literature describes the use of NPs as a delivery system of drugs to increase the response to anticancer compounds (Roblero-Bartolon et al. 2015). A wide variety of organic and inorganic nano-constructs, such as liposomal, micellar, polymeric, silica and gold NPs, have been introduced to deliver high payloads of PS to desired sites, when combined with targeting processes. Advantages of using NPs include lower levels of the PSs used in treatment, increased selectivity, reduced side effects and reduced dark toxicity. In addition, peptide or antibody tags in NP systems can increase selectivity more efficiently and aid in controlling the size of the particle, which can influence better passive targeting through EPR effect and, therefore, increased cellular uptake (Mehraban et al. 2015).

ANTIBODY-MEDIATED SPECIFICITY

In an effort to increase PS accumulation specificity and reduce unwanted PDT PS and NP side effects, significant effort has been devoted towards the synthesis, and charac-terization, of bio-conjugates. Synthesis with either NPs or PSs further enhances PDT NP-PS passive drug delivery by actively and specifically targeting tumourous cells with monoclonal antibody

(mAb) conjugates. In the case of anticancer-mediated PDT, malignant cells present different types, as well as greater amounts, of many surface antigens (Abrahamse and Hamblin 2016). Antibodies against TAA (tumour-associated antigens) are easily generated, and if correctly attached to a PS drug delivery system, the PS can be directly targeted and absorbed via cell membrane endocytosis into specific tumours and therefore causes targeted cancer cell death upon PDT light activation (St Denis et al. 2013).

PS TARGETING OF CRC AND CRC STEM CELLS

Although some PSs used in PDT reveal certain tumour selectivity by the EPR effect, they can also accumulate in healthy tissues causing side effects such as phototoxic and photoallergic reactions (Varol 2015). To avoid this complication, targeted photo-dynamic therapy (TPDT) was fashioned to improve PS drug delivery to cancer tissue, and the overall specificity and efficiency of PDT was increased (Kawczyk-Krupka et al. 2015). TPDT can be divided into two mechanisms of action: passive or active targeting. Passive PDT targeting makes use of the PSs drug carrier's physicochemical factors, as well as the morphological and physiological differences between normal and tumour tissue (i.e. EPR effect) to deliver the PS to a target site (Yoo and Ha,2012). Active PDT targeting involves PS drug delivery to a specific tumour site, which is based on a molecular recognition process, using specific ligands or antibodies which bind to overexpressed cancer cell receptors (Kawczyk-Krupka et al. 2015).

Table 4. PDT in clinical trials-oncology

Photosensitizer	Clinical trial phase (ClinicalTrials.gov)		
	Phase I	Phase II	Phase III
Porfimer sodium (Photofrin)	Pancreatic cancer	Human head & neck cancer Cholangiocarcinoma	Esophageal and/or gastric cardiac cancer
Aminolevulinic acid (5-ALA)	Early stage head & neck tumors Multple basal cell carcinomas Colon cancer	Malignant gliomas Basal cell carcinoma	
Verteporfin	Brain tumors	Age – related macular degeneration	
mTHPC (Foscan)	Non-small cell lung cancer	Nasopharyngeal carcinoma Cholangiocarcinoma	
TOOKAD	Renal tumors		

ANTIBACTERIAL PDT

APPLICATION OF PHOTODYNAMIC THERAPY *IN VITRO*

The impact of with photosensitizers (XF73, XF70,CTP1) on strains of *S. aureus* resistant to methicillin (MRSA) was investigated. The findings showed that concentrations (0.005 μM) of photosensitizers, using light (13.7 J/cm^2) for 10 minutes is effective to reduce a 3log$_{10}$ (> 99.9%) of bacteria (Maisch et al. 2005). In another study the bacte-ricidal effects of the photodynamic inactivation with a porphoporphyrin photosensitizer at 624 nm wavelength with an energy density of (0.2 J/cm^2) on 40 clinical isolates of MRSA and 40 clinical isolates of MSSA isolated patients admitted to the hospital in Gdansk was evaluated. The results of the study indicated the reduction of 3log$_{10}$ in the number of bacteria (Grinholc et al. 2008). Another study evaluated the impact of PDT using photosensitizers MB (3mM) and gallium-aluminium lasers at a wavelength of 660 nm red light with an energy density and time of 35 mW, 10 J, and 285 seconds, on *S. aureus*. The findings showed the number of bacteria (4.89-6.83 log10 CFU/mL) decreased in relation to the initial concentration of bacteria (Miyabe et al. 2011). Also the effect of photodynamic therapy using a protoporphyrin 25 μM photosensitizer with laser radiation at a wavelength of 624 nm on the MRSAstrains

and MSSA strains was evaluated. The results of this study indicated that there was a reduction of 0-3 log10 and 0.2-3 log10 strains of MRSA and MSSA in the number of bacteria, respectively (Grinholc et al. 2008). Sharma assessed the effectiveness of aPDT on *S. aureus* biofilm formation. In this study, a TBO photosensitizer was used at concentrations of 10-80 μm and light source diode laser with a 640 nm wavelength. The results showed that at 40 μM concentration, biofilm was destroyed and has the least cytotoxic effect in cells (Sharma et al. 2008). Li investigated the effect of photo-dynamic therapy with 5-amino-levulinic acid (ALA) photosensitizer and a concentration of 40 mM and an optical source laser with 635 nm wavelength for activating ALA at doses (0, 100, 200, 300 J/cm2) used. The results of this study showed that ALA without exposure to light or red light does not affect bacterial biofilm. However, a significant number of cells in the biofilm was inactivated during radiation with different doses of red light in the presence of 5-aminolevulinic acid, and at the dosage of 300 J/cm2, all bacteria (99.99%) were killed (Li et al. 2013). Some scientists reported the effect of laser light on MRSA strains using TBO photosensitizer at a concentration of 50 μg/mL and a HeNe laser light with a wavelength of 632.8 nm in 1, 5, 10 minutes. The findings of the study indicated that 100% of the bacteria were killed in 15 minutes. Antibiotic resistance patterns of these strains were different before and after laser radiation, so that they were resistant to gentamicin 10 μg prior to the laser irradiation, and had an intermediate resistance to vancomycin. Moreover, after laser radiation, they became sensitive to both these antibiotics (Hajim et al. 2010). Another study showed the effect of photodynamic therapy on clinical isolates of MRSA strains and *S. aureus* strain ATCC 25923 under the conditions of using TBO photosensitizer at concentrations (80-400 μM) and Pl-ce6 at a concentration of (8 μM) and an optical source of laser 600 nm wavelength with doses (10-30 J/cm2) for 30 minutes. The results of this study showed that Pl-ce6 and TBO at the concentration (8 μM, 30 J/cm^2 – 80 μM, 30 J/cm^2) induced killing of MRSA (4log10 and 3log10) and *S. aureus* (ATCC 25923 (3log10-2log10)) (Tang et al. 2007).

For Gram negative bacteria – the photodynamic inactivation influence on *Escherichia coli* (ATCC25922) and clinical resistant strains of *E. coli* using photosensitizers of MB and toluidine blue O (TBO) was studied (Kashef et al. 2012). MB (50 μg/mL) with a laser light of red (163.8 J/cm^2) capable of reducing 53.1% and 37.6% in the number of viable *E. coli* (ATCC25922) and drug resistant *E. coli* (the initial number of bacteria was 10^4-10^5 Cfu/mL). Moreover, TBO (50 μg/mL) and a laser dose of 46.68 J/cm^2 killed 98. 2% and 83. 2% of *E. coli* (ATCC25922) and drug-resistant *E. coli*. In another study, the photodynamic efficiency on the plankton condition in *Acinetobacter bau-mannii* was evaluated. The results showed that the decreasing in the number of *A. baumannii* in plankton condition was 2-3log$_{10}$ reported after photodynamic inactivation with 2 photo-sensitizers of TBO and MB (Ragas et.al2010). The efficacy of photodynamic therapy on *A. baumannii* was assessed in another study – the findings showed the reducing in logarithmic growth of live cells after photodynamic inacti-vation with MB and TBO (TBO) for 5 strains of *A. baumannii* was between (1.3 log$_{10}$), (3.5-2.4 log$_{10}$), (2.9-2.2 log$_{10}$) and (2.6 log$_{10}$). Further-more, photodynamic inactivation reduced the minimum inhibitory concentrations of growth inhibitors into Azithromycin, Imipenem, Cipro-floxacin and Gentamicin antibiotics (Kashef et al. 2014). A photodynamic test of 2 photo-sensitizers of TBO and meso-Tetra(N-methyl-4-pyridyl) porphine tetra tosylate (TMP) at a concentration of 5 mg/mL on 5 strains of *Pseudomonas aeruginosa* isolated from cystic fibrosis was performed, and the laser light killed 99.99% of bacteria (Donnelly et al. 2007).

Another study determined the efficacy of sub-lethal photodynamic therapy with the ability to form biofilm and the metabolic activity of *Enterococcus faecalis* under *in vitro* condi-tions by using indocyanine green photosen-sitizer at concentrations (2 mg/mL) and TBO and MB at a concentration of 0.2 mg/mL with a diode laser as light source for TBO and MB and indocyanine green were 635 nm-200 mW, 660 nm-150 mW, 810 nm-200 mW, respectively. The findings showed that PDT-ICG and PDT-MB and TBO-PDT sub-lethal reduces 42.8%, 22.6%, and 19.5% of biofilms, the sub-lethal dose of PDT-ICG and PDT-MB and TBO PDT reduced 98%, 94%, 82% of metabolic activity in *Enterococcus* spp., respectively (Pourhaji-bagher et al. 2016). In another study the effect of photodynamic therapy on *E. faecalis* in

biofilm formed at root infections under the laboratory conditions was investigated. The findings of the study suggest that 97% of the bacteria were reduced when they were exposed to red laser light and MB at a concentration of 25 mg/mL (Soukos et al.1998).

IN VITRO AND CLINICAL EFFECTIVENESS OF ANTIMICROBIAL PHOTODYNAMIC THERAPY (APDT)

Photodynamic therapy is effective against bacteria, viruses, fungi, and parasites but its inactivation efficiency varies according to the microorganism. In general, bacteria and viruses are more easily inactivated than fungi and parasites. Spores of bacteria and fungi, particularly endospores, and parasite eggs and cysts are more resilient to inacti-vation than the corresponding vegetative cells (Almeida et al. 2011).

BACTERIA SENSIBILITY

Gram-positive bacteria are more laser- sensitive than Gram-negative bacteria (Grinholc et al. 2008, Almeida et al. 2011). The difference in the sensitivity of the two groups is related to their different cell wall composition. Most Gram-positive bacteria have a cell wall consisting of several layers of peptidoglycans, negatively charged, which exhibit a relatively high degree of porosity. Macromolecules having a molecular weight of 30,000-60,000 (like glycopeptides and polysaccharides) can easily pass through this structure. Consequently, most photo-sensitizers (PS) can go through their membranes, since its molecular weight gene-rally is situated between 1500 to 1800 Da (Jori et al. 2006). On the contrary, Gram-negative bacteria display in the cell wall, an additional highly organized outer membrane, which is external to the peptidoglycan layer. The asym-metric nature of the outer membrane is a conse-quence of the distribution of its phospholipids, proteins, lipoproteins, and negatively charged lipopolysaccharides (Maisch et al. 2004, Sharma et al. 2011, Sperandio et al. 2013) which do not allow the passage of various molecules into its interior. However, hydrophilic molecules of 600-700 Da can diffuse through the porins (Nikaido et al.1994).Gram-positive bacteria can be efficiently inactivated by neutral and anionic PS since the diverse PS can effortlessly go through their highly permeable cell wall. Yet, these PS are not effective against Gram-negative bacteria [Hamblin et al.,75], unless they are co-administered with external membrane disrupting agents such as $CaCl_2$, EDTA, and polymyxin B, which can lead to electrostatic repulsion and destabilize the cell wall (Jori et al. 2004). Gram-negative bacteria can be directly and effectively inactivated by cationic PS since these PS are able to bind to the negatively charged components of the outer membrane and allow a more effective interaction (Hamblin et al. 2002).

As stated above, the primary difficulty of killing Gram-negative bacteria using PDT is to achieve a good penetration of the PS inside the bacterial cell wall. However, different approaches aim to eliminate this problem by, for example, creating positively charged (cationic) PS or by coupling or combining the PS with positively charged entities such as poly-L-lysine (Sperandio et al. 2013, Sahu et al. 2014), polyethyle-nimine (Tegos et al. 2006) and polymyxin B nano-peptide (PMBN) (Nitzan et al. 1992).

VIRUSES SENSIBILITY

There are several studies that suggest that lipid-enveloped viruses are more susceptible to PDT (Costa et al. 2012). It is also suggested that different types of nucleic acids viruses (DNA and RNA) present different susceptibility to PDT, but the differences between RNA and DNA viruses are not only attributed to their nucleic acid type, but also to the composition of their capsids (Costa et al. 2012).The clinical trials of aPDT application to inactivate viruses has been successful. Neutral red/proflavine was effectively used to treat herpesvirus genital infection without relevant side effects (Moore et al.1972). Porphyrins were shown to be effective against Herpes virus, the Influenza virus, and the Papillomavirus (Perlin et al.1987). aPDT is already approved to sterilize plasma. Different viruses such as Hepatitis viruses, Parvoviruses, the West Nile virus, and HIV have been effectively inactivated by methylene blue (Mohr et al. 2004).

FUNGI AND PARASITES SENSIBILITY

Since fungi and parasite cells are larger when compared to bacteria and viruses, the amount of ROS needed to kill such a larger cell is much higher than is necessary to kill a bacterial cell or

a viral particle (Demidova et al. 2005). On the other hand, the eukaryotic cell structure makes aPDT effect more difficult to work for these micro-organisms than for bacteria and viruses. Unlike bacteria and viruses, fungi and parasites are compartmented cells and, consequently, whenever the cell wall and membranes are damaged by the ROS, the PS enter its interior. Similar to bacteria, fungi also have a cell wall, which is more permeable to external substances than Gram-negatives cell wall, but less than in Gram-positives (Cabral et al. 2019). Since ROS are highly reactive and have a short lifetime, the localization of the PS into the cell is very important, since the organelles located nearby to the PS have the highest probability of being affected.

However, effective inactivation of fungi and parasites has already been observed (Calzavara-Pinton et al. 2012). In fact, to obtain the effective inactivation of fungi and parasites, it is necessary to adjust both PDT conditions and increase the PS concentration and the light dose (Donnelly et al. 2007). What is interesting, *Candida* spp. are effectively inactivated by aPDT, but they are not as susceptible to PDT as several prokaryotic bacteria, including *Staphylococcus aureus* or *Streptococcus mutans* (Pereira et al. 2011).It was observed that aPDT is effective for inactivating parasites, but also requires a higher PS concentration and higher light doses than those required for bacteria and viruses. aPDT with different PS have been tested for the inactivation of *Leishmania* spp. (Morgenthaler et al. 2008) and *Plasmodium falciparum* (Grellier et al.1997). Cysts of *Colpoda inflate* and eggs of helminths like *Ascaris lumbricoides* and *Taenia* spp. were also successfully photo- inactivated (Alouini, 2001).

IN VIVO STUDIES PDT IN INFECTIOUS DISEASES – PDT APPLICATIONS FOR GRAM-NEGATIVE BACTERIA

Gram-negative bacteria are responsible for many life-threatening infections in humans, especially in elderly people, and they are often innately resistant (especially *P. aerugi-nosa*) to the most commonly used antibiotics, making the search for new antibacterial drugs and alternative therapies, such as PDT, very important (Sperandio et al. 2013). The PS molecule, for instance, has to bind to the bacterial cell (Malik et al.1982), most often to the cell plasma membrane (Ehrenberg et al.1985) so the PDT killing effect can take place (Nitzan et al.1992). Gram-positive bacteria and yeasts are affected by neutral or anionic metal-free porphyrins (Malik et al.1990), while Gram-negative bacteria are not. This resistance to photosensitization by Gram-negative bacteria with anionic porphyrins was widely reported in the literature of the 1980's (Sperandio et al. 2013, Malik et al.1982, Venezio et al.1985, Nitzan et al.1987). PDT of both Gram-negative *Escherichia coli* and *P. aeruginosa* with high concentrations of hemato-porphyrin derivative (HPD) or deuteroporphyrin (DP) combined with high intensities of illumination did not result in any bacterial inactivation (Sperandio et al. 2013, Malik et al.1982, Venezio et al.1985, Nitzan et al. 1987). In addition, *E. coli* was only sensitive to porphyrin and light after suffering a pretreatment with toluene, which then induced susceptibility of this Gram-negative bacteria to PDT with hematoporphyrin derivative (Boye et al. 1980). It is only when the inner membrane of *E. coli* is exposed that porphyrin can bind to this membrane (Sperandio et al. 2013, Boye et al. 1980). Knowing this and the fact that the polycationic agent polymyxin nonapeptide can disturb and disorganize the outer-membrane structure of Gram-negative bacteria (Vaara et al. 1983), scientists were able to successfully kill *E. coli* and *P. aeruginosa* with PDT mediated by deuteroporphyrin (DP) (Nitzan et al. 1987), what represented a true advance in photodynamic inactivation of Gram-negative bacteria. Nevertheless, neither of these results (Nitzan et al.1987, Boye et al. 1980) resolved the problem of Gram-negative bacterial resistance (Malik et al. 1992].

One approach to turn Gram-negative susceptible to PDT is to pre-treat them with ethylene diamine tetraacetic acid (EDTA). It is known that Gram-negative wild-type cells treated briefly with EDTA lose up to 50% of their lipopolysaccharide into the medium and become very sensitive to hydrophobic agents (Malik et al. 1992). In fact, cationic molecules can more easily bind to the cell wall of Gram-negative bacteria, which is negatively charged due to teichoic acid residues, for example (Bourre et al. 2010). The negatively charged LPS molecules also have a strong affinity for cations such as calcium (Ca^{2+}) and magnesium (Mg^{2+}), the binding of which is required for the thermo-

dynamic stability of the outer membrane (Hancock, 1984). Again, considering the physical arrangement of the LPS layer of the Gram-negative bacteria outer membrane, treatment with low concentrations of polycations that tend to bind tightly to the highly negatively charged surface and to displace divalent cations can be effective (Malik et al.1992). As previously stated, the combined exposure to PMBN, DP and light inhibited *E. coli* and *P. aeruginosa* cell growth (Nitzan et al.1987). In addition, it was stated the disappearance of plasmid super-coiled fraction of *E. coli* when post-treated by PMBN and DP (Nir et al. 1991).Finally, a disturbance in the outer membrane of Gram-negative bacteria must occur so porphyrins and phthalocyanines can act in their inner membrane. In that way, the permeabilizing agent PMNP can disrupt the outer membrane and allow the penetration of porphyrin, consequently enabling the photosensitization of Gram-negative bacteria (Fotinos et al. 2008). In addition, through the same mechanism, EDTA treatment combined with phthalocyanines inactivate those bacteria and consist in a promising photodynamic therapy (Malik et al. 1992).

CONCLUSIONS

A photodynamic therapy-PDT is a modern, very promising modality for both scientific research and clinical treatment of oncologic and infectious diseases. The most advanced experiments were performed on tissue level in colorectal cancer cells while the most common application is in dentistry and skin diseases.

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