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EVALUATION OF PORPHYRIN DERIVATIVE FOR PHOTODYNAMIC THERAPY

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Porphyrin derivative (PD) is used as a photosensitizer in the photodynamic diagnosis (PDD) and photodynamic therapy (PDT) of cancer. The antitumor effects of PD was designed and synthesized appropriately with tailored hydrophilicity and lipophilicity in the present paper. The new compounds were detected and their antitumor activity in vivo and in vitro was also investigated. It was shown that PD-011 displayed a characteristic long wavelength absorption peak at 635 nm. After being exposed to 635 nm laser irradiation, PD-011 could inhibit cell proliferation in Eca-109 cells in vitro. The growth of Eca-109 cells in BALB/c nude mice was significantly inhibited by PD-011 in vivo. It was found that PD-011 had excellent anti-tumor effect in vitro and in vivo, which could be considered as a potential photosensitizer of PDT in tumor treatment.

Keywords: Photodynamic Therapy; Photosensitizer; Tumor

1. INTRODUCTION

Though we crossed many milestones in the field of medicine and health care in eradicating some deadly diseases over the past decades, cancer remained a challenge, taking the lives of millions of people and having adverse effects on the quality of life of survivors. The main challenges in the cancer treatments are severe side effects when treatment affects healthy tissues or organs. Thus, there is an urgent need for developing accessible and affordable cancer treatment modalities. In this review, we discussed photodynamic therapy (PDT) as a promising alternative to the existing therapy as it is affordable and does not require hospitalization of the patient (Chilakamarthi et al. 2017).The usage of photosensitizers for therapeutic purpose has a long history in countries such as India, China, Egypt and eosin was the first photosensitizer reported to treat skin cancer. FDA approved Photofrin which is still being used in cancer therapy was purified from hematoporphyrin mixture by Doughtery's group (Figure 1). Hematoporphyrin and Photofrin are considered as first generation PS. Photofrin has been approved in the treatment of lung cancers, bladder cancers, esophageal cancer and early stage cervical cancer. However, approved for a wide variety of cancer treatment, it has many drawbacks like lack of specificity, cutaneous phototoxicity, hydrophobicity and weak absorption in the therapeutic window (Dolmans et al. 2003).

The synthetic procedures of these PS are complex and difficult to get pure products. Photofrin is not soluble in water which is one of the important factors for biological use. Hence, continuous efforts are going on for designing and synthesizing more efficient water soluble, NIR absorbing PS.

In this context, the chemical characterization, photophysical properties, and photodynamic activities in vitro and in vivo of PD-011 are reported.

2. MATERIALS AND METHODS

All solvents and reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Solvent were removed by rotary evaporation under reduced pressure, and silica gel chromatography

was performed using silica gel H (300 - 400 mesh). UV-vis absorption spectrum was recorded on an ultraviolet visible spectrophotometer (Model V-530, Japan). Fluorescence spectra were measured on a fluorescence spectrophotometer

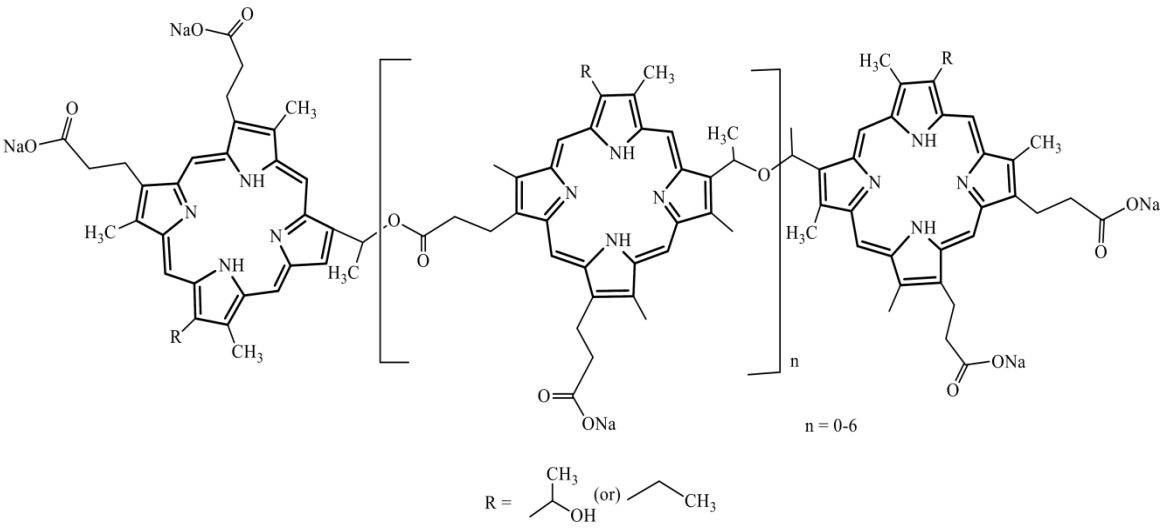

Fig 1. First generation photosensitizer, Photofrin®.

(FluoroMax-4, France).

2.1. UV-visible Absorption and emission spectra

UV-visible absorption spectrum was recorded on an ultraviolet visible spectrophotometer (Model V-530, Japan). Fluorescence spectra were measured on a Fluorescence Spectrophotometer (FluoroMax-4, France). Slits were kept narrow to 1 nm in excitation and 2 nm in emission. All the measurements were carried out at room temperature in quartz cuvettes with path length of 1 cm. All compounds were dissolved in DMSO, then they were diluted in different concentration and measured it.

3. IN VITRO EXPERIMENTS

3.1.Cell line and culture conditions

Eca-109 cells were obtained from the Type Culture Collection of the Chinese Academy of Sciences. All cell culture related reagents were purchased from Shanghai Ming Rong Bio-Science Technology Co., Ltd. Cells were cultured in normal RPMI-1640 culture medium. All media were supplemented with 10% fetal bovine serum (FBS), 100 units/mL penicillin G and 100μg/mL streptomycin. All cells were incubated at 37℃ in 5% CO2 in a humidified incubator. (Liao al. et 2016)

3.2. MTT cell viability assay

Eca-109 cells were cultured in RPMI-1640 medium with 10% (v/v) FBS, then they were harvested and seeded in 96-well plates at 2×104 cells per well. The cells were allowed to attach to the bottom of the wells for 24 hours before starting the experiment at 5% CO2 at 37℃. (Marks et al. 1992) PD-011 was administered to cells and allowed to uptake for 24 hours to test dark toxicity. Then RPMI-1640 medium containing drugs was removed and cells were washed with fresh PBS before irradiation with different light doses (ranging from 1 to 16 J cm-2) using an Nd:YAG laser at 635nm when the phototoxicity was tested at 10μM. The cell viability was evaluated by MTT colorimetric assay 24 hours after treatment.

3.3. In vivo pdt efficacy

PD-011 were injected to Five-week-old BALB/c nude mice bearing Eca-109 tumors via the lateral tail vein at a dose of 5mg/kg in 0.2 mL solution. PDT was performed following injection with laser light (635 nm, 180 J/cm2, 150 mW / cm2). Visible tumors were measured using two orthogonal measurements L and W (perpendicular to L), and the volumes were

calculated using the formula V = LW2/2 and recorded.

4. RESULTS AND DISCUSSION

4.1.UV–Vis absorption and fluorescence spectra

PD-011 displayed photosensitivity characteristic Soret and Q-band absorptions at 405 nm (Soret), and 635 nm (Q-band), respectively. Meanwhile, when excited at 405 nm, PD-011 showed the strongest mission peaks at 637 nm.

4.2. Cytotoxicity on Eca-109 cells

The effect of porphyrin derivative on the viability of cultured Eca-109 cells was evaluated by MTT assay. The results indicated that the PD-011 had the most medicinal properties with low dark toxicity and high phototoxicity.

4.3. In vivo photodynamic antitumor potency

The PDT anti-tumor efficacy of PD-011 was evaluated in Eca-109 tumor bearing BALB/c nude mice. By comparing the tumor weight in different groups, the inhibition rates of tumor growth could be calculated. When tumor sizes had reached 6-8 mm in diameter, the mice were given intravenous injection via tail vein at a dose of 5 mg/kg. After 4 h incubation, the tumor site was irradiated with laser light (635 nm, 180 J/cm2, 150mW/cm2). After five days of administration, treatment effects became significant. The volume of tumors in three sets of parallel control group was larger than that in Laser+ PS group. The tumor volume increased about 10 folds for 14 days in control group.

5. DISCUSSIONS

In this paper, we show how photodynamic treatments affect Eca-109 tumor cells with PD-011. The photodynamic activities were evaluated in vitro and in vivo. The PD-011 played a characteristic long wavelength absorption peak at 635 nm. PD-011 induces no low dark toxicity and high photo-toxicity in the range of concentrations used in the present photodynamic studies in vitro.

In vivo therapeutic efficacy of PDT by using PD-011, after being exposed to 635nm laser light irradiation, the growth of Eca-109 tumor cells in BALB/c nude mice was significantly inhibited. Therefore, PD-011 is a promising antitumor photosensitizer for photodynamic therapy.

6. ACKNOWLEDGMENT

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