Photodiagnosis and Photodynamic Therapy 42 (2023) 103142

Contents lists available at ScienceDirect

Photodiagnosis and Photodynamic Therapy

journal homepage: www.elsevier.com/locate/pdpdt

Combination of photodynamic antimicrobial chemotherapy and ciprofloxacin to combat *S. aureus* and *E. coli* resistant biofilms

Yolande Ikala Openda, Tebello Nyokong *

Institute for Nanotechnology Innovation, Rhodes University, Makhanda 6140, South Africa

ARTICLE INFO

Keywords:
Cationic photosensitizers
Photodynamic antimicrobial therapy
Ciprofloxacin
Biofilms
Dual therapy

ABSTRACT

Photodynamic antimicrobial chemotherapy (PACT) coupled with an antibiotic, ciprofloxacin (CIP), was investigated using two indium metallated cationic photosensitizers, a porphyrin (**1**) and a phthalocyanine (**2**). Applying PACT followed by the antibiotic treatment led to a remarkable reduction in the biofilm cell survival of two antibiotic-resistant bacterial strains, *S. aureus* (Gram-positive) and *E. coli* (Gram-nenative). Treating both bacteria strains with PACT alone showed no significant activity at 32 μM with 15 min irradiation, while CIP alone exhibited a minimum biofilm inhibition concentration (MBIC) at 4 and 8 μg/mL on *S. aureus* and *E. coli,* respectively following 24 h incubation. The combined treatment resulted in the complete eradication of the matured biofilms with high $\log_{10}$ reduction values of 7.05 and 7.20 on *S. aureus* and *E. coli,* respectively, at low concentrations. It was found that 15 min PACT irradiation of 8 μM of complexes (**1** and **2**) combined with 2 μg/mL of CIP have a 100% reduction of the resistant *S. aureus* biofilms. Whereas the total killing of *E. coli* was obtained when combining 8 μM of complex **1** and 16 μM of complex **2** both combined with 4 μg/mL of CIP.

1. Introduction

The prevalence of a wide range of pathogens resistant to current antibiotics remains a major healthcare problem, especially when bacterial infections are established as biofilms [1,2]. Bacterial biofilm cells are found to be resistant to conventional antibacterial treatment due to the heterogeneous structure of the exopolymeric matrix (EPS) which protects the bacteria living within a biofilm against the host's immune mechanisms and antimicrobial agents. This protective layer displays phenotypic traits not observed in the free-floating planktonic cells [3]. This particularity induces the increased potential of multidrug resistance.

Bacteria such as *Staphylococcus aureus* and *Escherichia coli* strains are well known to adhere to biological or medical devices' surfaces and produce strong biofilms which may lead to the occurrence of serious complications and chronic infections [4]. Hence, researchers have been putting efforts into finding efficient ways to eradicate biofilms with alternative methods of treatment, such as photodynamic antimicrobial chemotherapy (PACT) [5,6].

PACT has garnered promising results in recent decades for treating bacteria-causing infections [1,7–10]. The treatment in PACT depends on three critical parameters that determine its efficacy: photosensitizer (PS), light, and oxygen [7,11,12]. During treatment with PACT, a PS molecule is excited by light of a specific wavelength in the presence of molecular oxygen, leading to the production of reactive oxygen species (ROS) which could kill bacteria by oxidative damage of their biomolecules or cause impairment of the protein synthesis process that induces DNA mutation [7–10,13,14]. This multitargeted nature of ROS enables PACT to inactivate bacteria regardless of their antimicrobial resistance levels and mechanisms [15,16]. Furthermore, this mechanism is highly selective with rapid bacterial killing and is minimally invasive without the possibility of bacterial resistance [5,6].

Associating PACT with conventional therapies such as antibiotics is emerging as an effective and rapid response against multidrug-resistant bacteria [17–20]. This approach brings both individual advantages together and improves bacterial reduction while using lower dosages of PS and antibiotics. In this study, we aimed to investigate the individual effect of PACT and antibiotics on biofilms and their synergistic effect when subsequently administered.

There are several reports on PACT/antibiotic combinations [7]. The PSs used include porphyrin and its derivatives [21–23], methylene blue [18], 5-aminolevulinic acid [24], etc. PACT activity of porphyrins has in particular been studied in the presence of ciprofloxacin (CIP) [22] which is a subject of this work. Such studies do not exist for phthalocyanines. In

* Corresponding author.
E-mail address: t.nyokong@ru.ac.za (T. Nyokong).

https://doi.org/10.1016/j.pdpdt.2022.103142
Received 9 June 2022; Received in revised form 13 September 2022; Accepted 29 September 2022
Available online 1 October 2022