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Immunomodulatory effect of new quinolone derivative against cisplatin/gamma radiation-induced renal and brain toxicity in mice

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ABSTRACT

Treatment of cancer often requires exposure to radiation, which has several limitations involving non-specific toxicity toward normal cells, reducing the efficacy of treatment. Recent studies synthesize new quinolone derivatives to satisfy other purposes such as treatment of inflammatory and malignant diseases. The main purpose of the present study is to evaluate the effect of a new quinolone derivative; 2-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2-oxoacetic acid (EHQA) and its possible mechanism against gamma radiation (IRR) and cisplatin (Cis) induced nephrotoxicity and neurotoxicity in mice. The structure of the newly synthesized quinolone derivative was elucidated by microanalytical and spectral data, which were found consistent with the assigned structures. Exposure to Cis and IRR significantly induced renal damage manifested by a significant increase in levels of urea and creatinine. Moreover, the exposure to both Cis and IRR significantly decreased the levels of anti-apoptotic protein; Bcl-2 in both renal and brain tissue homogenate accompanied by activation of an inflammatory marker; IL-17. Immunophenoting results showed an activation of T- lymphocytes marker; CD3 and B-lymphocytes marker; CD19. Interperitonial administration of EHQA significantly ameliorated the above-mentioned parameters. Overall, the present results indicated that EHQA is a promising anti-inflammatory and anti-apoptotic agent. From the obtained results it can be concluded that EHQA could be a candidate as immunomodulatory agents. Further studies are required to establish its molecular mechanism.

1. Introduction

Ionizing radiation (IR) has attracted a lot of attention due to its beneficial as well as possible harmful effects to human population. Application of ionizing radiation, over and above surgery, and chemotherapy, has been the treatment of choice in case of solid malignancies [1]. However, a substantial fraction of such tumors would fail to respond well to the radiation treatment, and require a very high dose to get killed, posing a severe limitation to the radiotherapy. Moreover, co-administration of radiation along with the chemotherapeutic regimen might aggravate these complications [2]. The deleterious effects of IR are due to generation of reactive oxygen and nitrogen species (ROS/RNS), which react with biological molecules and produce toxic free radicals [3,4].

Nephrotoxicity is the main side effect of treatment with chemotherapy and radiotherapy. The proximal tubular cells of the kidney are specifically damaged by an inflammation and fibrogenesis mechanisms including activated protein kinases and reactive oxygen species [5]. Several reports suggest that inflammatory mechanisms of kidneys include activation of NF-κB which promotes producing immune inflammatory mediators and increased expression of tumor necrosis factor alpha (TNF-α) in renal tubular cells, TNF-α activates proinflammatory cytokines such as interleukin-1, 4, 6 (IL-1β, IL-4, IL-6) and transforming growth factor-β1 (TGF-β 1) [6].

Another serious side effect of chemotherapy and radiotherapy is neuropathy, which appears as tinnitus, hearing loss, loss of vibration sense, paresthesia, and weakness [7,8]. Exposure to chemotherapy and ionizing radiation leads to apoptosis in neurons by enhancing the expression of pro-apoptotic Bax protein and suppressing the expression of anti-apoptotic Bcl2 protein in the neurons [9,10] while, the injury pathway takes place by forming DNA adduct DNA in dorsal root ganglia neurons, leading to apoptosis of the neurons [11].

Quinolones is a large family and extending synthetic compound. Naphthyridine agent, nalidixic acid was the first of these compounds to be discovered [12]. Flourination at position 6 of nalidixic acid yielded a new compound; flumequine, which improve the activity of nalidexic acid against gram-positive bacteria [13]. Then new derivatives of flouroquinolones appeared as antibiotics such as Ciprofloxacin3,

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trovafloxacin, moxifloxacin, gatifloxacin, gemifloxacin and grepafloxacin, with antibiotic improved activity [14]. Development and utilization of some of these newer agents, trovafloxacin, gemifloxacin and grepafloxacin, has been restricted or suspended because of adverse drug reactions [15]. However, some synthesized quinolones such as fleroxacin was the first fluoroquinolone antibiotic reported to offer protection against aminoglycoside-induced nephrotoxicity [16]. Moreover, new generation of non- fluorinated quinolones was developed to achieve different aims other than treatment of microbial diseases such as Linomide (Roquinimex), a quinoline-3-carboxamide which is immunomodulatory and antitumor compound [17]. Consequently, the main object of the current study is to evaluate the anti-inflammatory effect of a newly synthesized non-fluorinated quinolone and its plausible mechanistic aspect against cisplatin (Cis)/ ionizing γ – radiation (IR) induced nephro- and neurotoxicity.

2. Materials and Methods

2.1. Chemicals and Reagents

Cisplatin and all chemicals and reagents used in this study were of analytical grade and purchased from Sigma- Aldrich Chemical Co. (St. Louis, MO, USA).

2.2. Preparation of New Quinolone Derivative

The synthesis was carried out by the method of Abass et al. [18]. Briefly, the reaction was started with of 3-acetyl-4-hydroxyquinolin-2(1H)-one (EAHQ) to yield difluoroboryl complex of 3-acetylquinolinones (EAFQ) which converted to the expected compound 2-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2-oxoacetic acid (EHQA) via an oxidation reaction Fig. 1.

2.3. Elucidation of Structure of EHQA

Melting points are uncorrected and were determined in open capillary tubes on a digital Stuart-SMP3 melting point apparatus. Infrared spectra were recorded on a Perkin- Elmer FT-IR 1650 spectrophotometer, using samples in KBr disks. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded on Mercury–300BB or Gemini–300BB spectrometers (δ), using DMSO-d_6 or CDCl3 as solvents and TMS as an internal reference. Mass spectra (70 eV) were obtained using a Shimadzu GC-2010 Gas–Chromatography instrument mass spectrometer. Elemental microanalyses were performed on a Perkin-Elmer CHN-2400 analyzer.

2.4. Determination LD50 of Quinolone Compound by Interpertonial Injection in Swiss Albino Mice

White male albino mice weighing between (20–25 g) purchased from the Egyptian Organization for biological products and vaccines, VACSERA, Egypt. Mice were housed in plastic airy cages under controlled environmental condition cycle (12 h dark, 12 h light at 250C) in groups of 5 animals per cage with free access to food and water. The procedure was carried out according to Bass et al. [19]. For the determination of acute lethal dose (LD100) and median lethal dose (LD50) of EHQA, doses from 50 to 200 mg/Kg body weight with increasing factor (1.15) were used. Mortality was recorded after 24 h, and LD50 was calculated as following:

Log LD_{50} = Log LD next below 50% + (Log increasing factor x proportionate distance).

$$\textbf{Proportionate distance} = \frac{50\,\% \text{ - mortality next below } 50\,\%}{\%\text{ mortality above } 50\,\% \text{ - mortality next below } 50\,\%}.$$

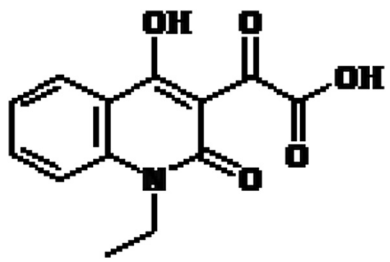

Fig. 1. The expected structure of compound 2-(1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)-2-oxoacetic acid (EHQA).

2.5. Radiation Process

Whole-body gamma-irradiation was performed at the National Center for Radiation Research and Technology (NCRRT), Atomic Energy Authority, Cairo, Egypt, using Cell-40 biological irradiator (137Cesium), manufactured by the Atomic Energy of Canada Limited, Ontario, Canada. The radiation dose rate was 0.456 Gy/min at the time of exposure. The total radiation dose was 2Gy as a single dose of the whole body. Animals were not anesthetized before irradiation.

2.6. Experimental Animals

Male albino mice weighing (20–25 g) were purchased from the Egyptian Organization for biological products and vaccines, VACSERA, Egypt. Mice were housed in controlled environmental condition cycle (12 h dark, 12 h light at 250C). The animals were maintained on a commercial standard pellet diet and tap water ad libitum. Animal maintenance and treatments were conducted in accordance with the National Institute of Health Guide for Animal, as approved by Institutional Animal Care and Use Committee (IACUC).

2.7. Experimental Design

2.7.1. Animal Groups

Forty mice were divided into four equal groups with ten animals per group as follows:

Group 1 (Control):	Mice were served as normal control.
Group 2 (Q):	Mice were injected interpretonialy with EHQA suspended in distilled water solution (14 mg/kg b.wt daily for 15 days).
Group 3(CR):	Mice were injected interpretonialy with 1 mg/Kg/day of cisplatin daily for 5 days according to Sawhney et al. [20], then mice on day 5th were subjected to single dose of gamma radiation; 2 Gy.
Group 4 (CRQ):	Mice were injected with EHQA as in group 2 for 10 days, then on day 11th mice were injected with cisplatin and exposed to IR as group in 3 parallel with EHAQ 5 days later.

All animals were sacrificed 24 h after the radiation, animals were anesthetized with diethyl ether and heparinized blood was collected, centrifuged at 3000 rpm for 20 min and plasma was stored at −20 °C for biochemical assay. Whole spleen, kidney and brain tissues were excised and weighed 10% (*w/v*) tissue homogenates was prepared in saline. The homogenates were centrifuged at 10,000*g* for 15 min and aliquots of supernatants were separated and used for the different biochemical assays.

2.8. Biochemical Investigation

2.8.1. Determination of Kidney Function in Plasma

Plasma creatinine and urea were determined enzymatically using