Gold-containing compound A8 (A8GC) Inhibits the growth of MCF-7 estrogen-positive breast cancer by inducing apoptosis

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Introduction

Breast cancer is the most prevalent type of cancer worldwide and in Saudi Arabia. In Saudi Arabia prevalence rate of breast cancer reached %22 and considered the most common cancer and it's increasing in all over the country. Breast cancer is a complex disease that classified to Hormonal-receptor+, Overexpressed HER2 and triple-negative breast cancer. MCF-7 is a cell line that has overexpression of estrogen receptor (estrogen+),

A8 is a yellow solid of the gold (III) (A8GC). This complex has distorted square planar through Au (III) center atom and it is stable in light and air. We hypothesize that A8GC induces its anti-tumor effect by DNA damage and apoptosis

Objectives

The aim of this study is to elucidate the mechanism of action involved in the anti-cancer effect of "A8-Gold-Containing compound (A8GC) on MCF-7 cell line. Which will be fulfilled as follows:

- Cytotoxicity evaluation of "A8GC" on MCF-7 cell line.
- Investigate the potential effect of A8GC compound on autophagy, DNA Damage, and apoptosis in MCF-7 cell line.

Methods and Materials

MCF-7 cell line cultured directly in DMEM, supplemented with 10 % fetal bovine serum (FBS), with 1 % streptomycin/penicillin. The maintenance of the cell lines at 37ºC and 5% CO_2, and 95% humidified incubator.

For induction of autophagy, DNA Damage, and apoptosis, MCF-7 seeded in 6 well plate, then incubated for 24 hrs. then treated with different concentrations of A8GC (1,5. and 10 µM) for 24 h. Then A8-treated MCF-7 was evaluated after 24 hrs using Muse® Cell Analyzer.

For determination of A8-induced autophagy, MCF-7 cells were treated with 1 and 5 µM A8GC for 24 h in 6 well plate then washed one time by 1X PBS. Acridine Orange solution (Santa Cruz Biotechnology) 1 µg/ml was added to each well and incubated for 30 min at 37º C under humidified environment. Finally, cells were washed by 1X PBS and the morphological changes of autophagy were detected under fluorescence microscope as described previously.

Results

A8GC failed to induce autophagy as indicated by slight positive acridine orange staining even at concentration of 5 µM compared to our control, whereas clear accumulation of autophagosomes was remarkably observed in cells treated with serum free medium. In addition, serum free medium cells showed morphological markers of autophagy such as enlargement while A8GC-treated cells demonstrated features of cell death, probably apoptosis (Fig1).

The induction of apoptosis of A8GC was evaluated after 24 hrs. We used (control, 1 µM, 5 µM). The total percentage rate of early apoptosis and late apoptosis for MCF7 was 1.68 ± 0.33 %, 56.78 ± 1.5 %, and 70.07 ± 0.42, respectively. The observed apoptotic effect was compared to the control. It is clearly that A8GC induces apoptosis at subtoxic dose.

The induction of DNA damage of A8GC was evaluated after 24 hrs. We used (control, 1 µM, 5 µM). The total percentage rate of early apoptosis and late apoptosis for MCF7 was 5 ± %, 8 %, and 27%, respectively. The observed DNA damage effect was compared to the control.

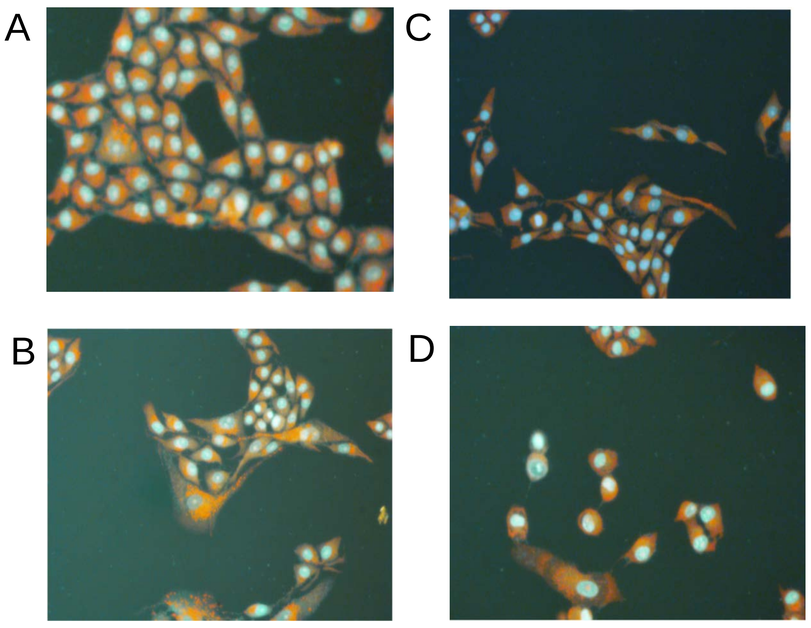

Figure 1 : Effect of A8GC on autophagy. MCF-7 cells were treated for 24 h with A8GC (A) 0 µM, B) 0 µM serum free medium, (C)1 µM, and (D)5 µM.

IC50 in µM	
	MCF-7
Cisplatin	>100
A 8	2.7(0.01)

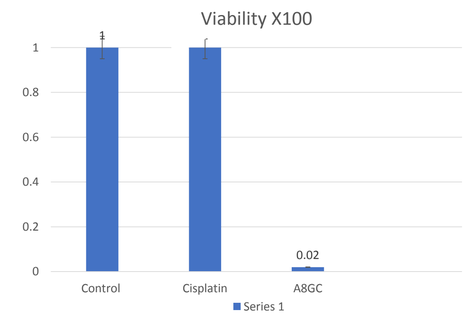

Chart 1. Comparing A8GC with standard chemotherapy (cisplatin) by cell viability test (MTT assay).

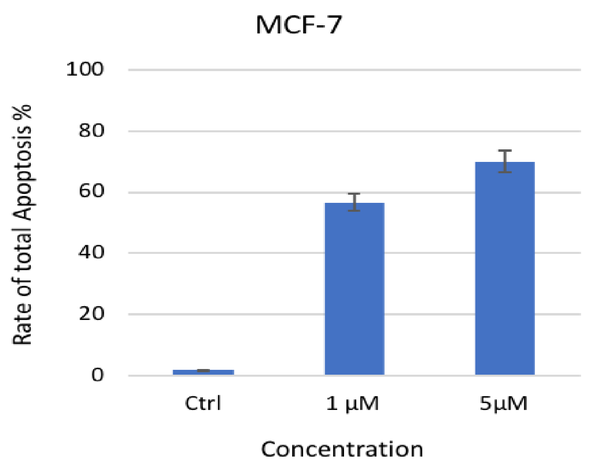

Chart 2. The observed apoptotic effect was compared to the control (control, 1 µM,5 µM).

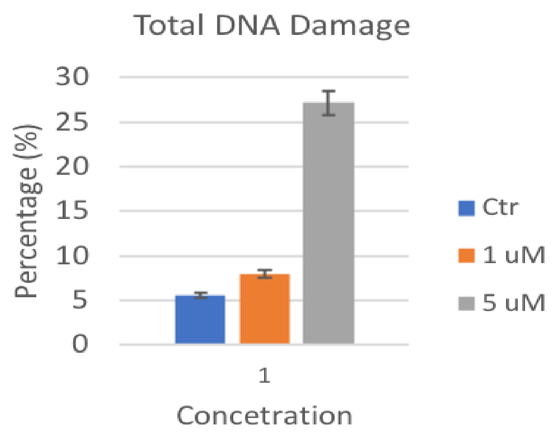

Chart 3. The observed DNA damage effect was compared to the control (control, 1 µM,5 µM).

Discussion

In order to better understand the mode of A8GC induced cytotoxicity in MCF-7 cells, we had to consider the most prevalent mode of cell death and/or growth arrest that can be promoted during the exposure to chemotherapy and/or radiotherapy.

A8GC clearly induces apoptosis. This could attribute to the ability of A8GC to bind to DNA and cause double-strand DNA break (DNA damage).

In addition to apoptosis, reports have proven that autophagy can be induced in cancer therapy.

Although apoptosis is the most desirable effect, autophagy has been also considered as another mode of anticancer-induced cytotoxicity. Our data here did not suggest that autophagy was promoted upon exposure to A8GC. However, apoptosis was clearly increased in response to A8GC treatment. Taken together, our treatment paradigm seems to shift cells toward apoptosis rather than toward autophagy.

Conclusions

In conclusion, as the results showed A8GC is an effective and a potent metal-containing compound that has anti-cancer effect against MCF-7 estrogen-positive breast cancer. It inhibits the growth of MCF-7 and induces apoptosis and DNA damage.

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References