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Cytotoxic effects of *Tetraselmis suecica* chloroform extracts with silver nanoparticle co-application on MCF-7, 4 T1, and Vero cell lines

Hanaa Ali Hussein [1,2] · Habsah Mohamad [1] · Maziah Mohd Ghazaly [3] · A. A. Laith [4] · Mohd Azmuddin Abdullah [1]

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Abstract

In the present study we evaluated the effects of silver nanoparticles (AgNPs) and *Tetraselmis suecica* chloroform (CHL) crude extracts as single and co-applications against MCF-7 and 4 T1 breast cancer cells and normal Vero cell-lines. The AgNPs single application exhibited the highest cytotoxicity in a dose-dependent manner with IC_{50} of 5.3, 17.78, and 25.11 μg mL^{-1} against MCF-7, 4 T1 and Vero cell lines, respectively, after 72 h treatments. The AgNPs-*T. suecica*-CHL co-application at 2:1 ratio achieved the IC_{50} of 6.60 and 53.7 μg mL^{-1} on MCF-7 and 4 T1 cells, respectively, while the *T. suecica*-CHL single application only showed the IC_{50} of 46.77 and 83.17 μg mL^{-1}, respectively. However, both the *T. suecica*-CHL and AgNPs-*T. suecica*-CHL showed no cytotoxic activity against the Vero cells. The AgNPs-*T. suecica*-CHL exhibited the highest late apoptotic events on MCF-7 (38.8%), followed by Tamoxifen (TMX), AgNPs and *T. suecica*-CHL. The cell cycle analysis of AgNPs-*T. suecica*-CHL–treated cells showed a significant increase in the accumulation of events at sub-G1 phase with increased ADP/ATP ratio and Caspase 3/7, suggesting the induction of apoptosis. The results brought new insights into the formulation of microalgal crude extracts (MCEs) and AgNPs co-applications in exerting strong cytotoxic effects on MCF-7 and 4 T1 cancer cells, but without having any cytotoxicity on the normal Vero cell-lines.

Keywords Microalgae · Natural product · Chlorophyta · *Tetraselmis suecica* · Silver nanoparticles · Co-application · Anti-cancer agent

Introduction

Breast cancer is the most common cancer in women around the world (Curado 2011) with the incidence rate (per 100,000 women) of 89.9 in Western Europe, more than 80 in developed countries (except Japan), but only 19.3 in Eastern Africa and less than 40 in most of the developing countries. The estimated rate could also be high in countries such as Latin America (Ferlay et al. 2015), due to the population aging and screening practices (Cao et al. 2008; Jung et al. 2009; Ferlay et al. 2015). The common therapies for cancer are surgery and chemotherapy. While chemotherapeutic agents may be effective against cancer cells, they may cause side effects on normal cells with consequences such as DNA damage, digestive problems, leukopenia, and hair loss as well as the possibility of drug resistance which reduces the effectiveness of chemotherapy (Rezakhani et al. 2014). Another major challenge is the poor water solubility of anti-cancer drugs as this may limit the activity of a compound and reduce the efficacy of an anti-cancer agent (Williams et al. 2013).

Nanotechnology can improve drug delivery and redirect chemotherapy or target the compounds directly to the cancer cells or stromal cell via both passive and active targeting strategies (Gul-e-Saba and Abdullah 2015). However, not all nanocarriers can penetrate cancer tissue (Lammers et al. 2012) as these are determined by their physical and chemical properties and the ability of drug penetration in tumor tissue (Minchinton and Tannock 2006; Zhang et al. 2012). The

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✉ Mohd Azmuddin Abdullah
azmuddin@umt.edu.my; joule1602@gmail.com

[1] Institute of Marine Biotechnology, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia

[2] College of Dentistry, University of Basrah, Basrah 00964, Iraq

[3] School of Fundamental Science, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia

[4] School of Fisheries and Aquaculture Sciences, Universiti Malaysia Terengganu, 21030 Kuala Nerus, Terengganu, Malaysia

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