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Concentration effects of grape seed extracts in anti-oral cancer cells involving differential apoptosis, oxidative stress, and DNA damage

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Abstract

Background: Grape seeds extract (GSE) is a famous health food supplement for its antioxidant property. Different concentrations of GSE may have different impacts on cellular oxidative/reduction homeostasis. Antiproliferative effect of GSE has been reported in many cancers but rarely in oral cancer.

Methods: The aim of this study is to examine the antioral cancer effects of different concentrations of GSE in terms of cell viability, apoptosis, reactive oxygen species (ROS), mitochondrial function, and DNA damage.

Results: High concentrations (50–400 µg/ml) of GSE dose-responsively inhibited proliferation of oral cancer Ca9-22 cells but low concentrations (1–10 µg/ml) of GSE showed a mild effect in a MTS assay. For apoptosis analyses, subG1 population and annexin V intensity in high concentrations of GSE-treated Ca9-22 cells was increased but less so at low concentrations. ROS generation and mitochondrial depolarization increased dose-responsively at high concentrations but showed minor changes at low concentrations of GSE in Ca9-22 cells. Additionally, high concentrations of GSE dose-responsively induced more γH2AX-based DNA damage than low concentrations.

Conclusions: Differential concentrations of GSE may have a differentially antiproliferative function against oral cancer cells via differential apoptosis, oxidative stress and DNA damage.

Keywords: GSE, Apoptosis, Oxidative stress, DNA damage, Oral cancer

Background

Betel quid chewing is one of the main causes leading to oral cancer in Taiwan [1]. Arecoline, one of main effective components in betel quid, was reported to lead to DNA damage and apoptosis through the formation of reactive oxygen species (ROS) and contribute to oral carcinogenesis [2-5]. Therefore, the modulation of ROS level may be helpful for oral cancer prevention and therapy.

Grape seed extract (GSE) is a common dietary health supplement due to its natural ROS modulating ability [6]. Commercial preparations of GSE are marketed in the world as a dietary health supplements due to their

natural free radical scavenging ability [6]. The cancer chemoprevention and anticancer potential of GSE has been well reviewed previously [7] including skin, colorectal, prostate, breast, lung, and gastric cancers. However, the GSE effects with respect to oral cancer cells are less studied as yet.

ROS modulation effect has been well reviewed [8,9]. For example, cellular ROS may regulate apoptosis through the mitochondrial pathway [10-13]. Pro-oxidants induce ROS specifically targeting cancer cells, thereby activating signal transduction pathways that are responsible for cell cycle arrest and/or apoptosis [14]. Similarly, GSE was reported to generate a strong superoxide radical-associated oxidative stress and result in the apoptosis of non-small-cell lung cancer cells [15] as well as in the induction of DNA damage [16].

Different concentrations of GSE were reported to generate diverse biological effects in several cancer studies

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