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# Synergistic anti-proliferative effect of resveratrol and etoposide on human hepatocellular and colon cancer cell lines

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abstract

Resveratrol is an active component of grape, which has been shown to inhibit proliferation of a wide variety of tumor cells. The ability of resveratrol to enhance anti-proliferative effects of etoposide in wild type p53 liver carcinoma (HepG2) and colon cancer (HCT-116) cells was investigated with focusing on p53 activation. HepG2 cells and HCT-116 cells were treated with resveratrol and/or etoposide in a time- and dose-dependent manner and their proliferative response was evaluated by XTT assay. The expression of p53 protein was assessed using Western blot. Resveratrol exerted anti-proliferative activity on both cell types in a dose (25–100 μM)- and time (24–72 h)-dependent manner. Interestingly in HepG2 cells, resveratrol exhibited the same levels of cytotoxicity as etoposide (10 μM) when the cells treated with Z 25 μM for 48–72 h. In contrast to HepG2, resveratrol significantly enhanced anti-proliferative effects of etoposide in HCT-116 cells. P53 expression was up-regulated by resveratrol and etoposide and pre-incubation of both cells with resveratrol increased levels of etoposide-induced p53 expression. In line with cytotoxicity effect, combination therapy showed stronger activation of p53 in HCT-116 compared to HepG2. It seems that resveratrol exerts differential synergistic effect with etoposide on proliferation of cancer cells from different origin which is mainly accompanied by p53 activation. Our data represent a future strategy to provide much safer and more effective treatment for colon cancer.



## 1. Introduction

Hepatocellular carcinoma (HCC) is a frequent malignancy worldwide with high prevalence (Blechacz and Mishra, 2013). Although surgery and non-surgical therapeutic modalities have been employed for treatment of HCC, such treatments are rarely curative and have marginal effect on survival rate. Therefore, development of more effective approaches is of great interest.

Although not as fatal as HCC, colorectal cancer (CRC) is one of the leading causes of death in men and women and globally ranks among the third most common cancers (Pan et al., 2011). The prevalence of CRC is increasing steadily despite deep understanding of its pathogenesis. It has been reported that almost 50% of patients with CRC will develop recurrent disease, indicating that currently available treatment regimens are not able to control this disease and there is an imperative need for improved therapies (Pan et al., 2011).

The most common modalities for cancer therapy include surgery, radiotherapy and chemotherapy. Although, chemotherapy is often used as a main regimen in the treatment of most cancers, chemoresistance represents a major obstacle in cancer therapy. Chemosensitization is among the strategies that are currently proposed for overcoming chemoresistance. It is based on the use of one drug to enhance activity of another one by modulating one or more mechanisms of resistance. Over the years, natural products have been discovered to be more effective than cancer drugs because of their multi-targeting property, low cost, low toxicity and immediate availability (Gupta et al., 2011). Phytochemicals are among the most promising chemopreventive and treatment options for the management of cancer. In this regard, resveratrol (trans-3, 4′, 5-trihydroxystilbene, $C_{14}H_{12}O_3$) (RSVL) could be viewed as an ideal molecule for

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