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Bioactive form of resveratrol in glioblastoma cells and its safety for normal brain cells

Xiao-Hong Shu[1,2], Hong Li[1], Xiao-Xin Sun[1], Zheng Sun[1], Li-Li Wang[1], Xue Song[1], Shun Shi[1], Mo-Li Wu[1], Xiao-Yan Chen[1], Qing-You Kong[1], Liu Jia[1]

[1]Liaoning Laboratory of Cancer Genetics and Epigenetics and Department of Cell Biology, Dalian Medical University, Dalian 116044, China; [2]Department of Medicinal Chemistry, College of Pharmacy, Dalian Medical University, Dalian 116044, China

Corresponding Author: Liu Jia, PhD, Professor, and Xiao-Hong Shu, PhD, Professor, Liaoning Laboratory of Cancer Genetics and Epigenetics and Department of Cell Biology, Dalian Medical University, Dalian 116044, China

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ABSTRACT

Background: Resveratrol, a plant polyphenol existing in grapes and many other natural foods, possesses a wide range of biological activities including cancer prevention. It has been recognized that resveratrol is intracellularly biotransformed to different metabolites, but no direct evidence has been available to ascertain its bioactive form because of the difficulty to maintain resveratrol unmetabolized in vivo or in vitro. It would be therefore worthwhile to elucidate the potential therapeutic implications of resveratrol metabolism using a reliable resveratrol-sensitive cancer cells.

Objective: To identify the real biological form of trans-resveratrol and to evaluate the safety of the effective anticancer dose of resveratrol for the normal brain cells.

Methods: The samples were prepared from the condition media and cell lysates of human glioblastoma U251 cells, and were purified by solid phase extraction (SPE). The samples were subjected to high performance liquid chromatography (HPLC) and liquid chromatography/tandem mass spectrometry (LC/MS) analysis. According to the metabolite(s), *trans*-resveratrol was biotransformed *in vitro* by the method described elsewhere, and the resulting solution was used to treat U251 cells. Meanwhile, the responses of U251 and primarily cultured rat normal brain cells (glial cells and neurons) to 100μM *trans*-resveratrol were evaluated by multiple experimental methods.

Results: The results revealed that resveratrol monosulfate was the major metabolite in U251 cells. About half fraction of resveratrol monosulfate was prepared *in vitro* and this *trans*-resveratrol and resveratrol monosulfate mixture showed little inhibitory effect on U251 cells. It is also found that rat primary brain cells (PBCs) not only resist 100μM but also tolerate as high as 200μM resveratrol treatment.

Conclusions: Our study thus demonstrated that *trans*-resveratrol was the bioactive form in glioblastoma cells and, therefore, the biotransforming activity of *trans*-resveratrol would be reversely correlated with the chemosensitivity of the treated cells. The findings from PBCs suggest that an effective anti-glioblastoma dose of resveratrol may not exert side-effect on normal brain cells, providing a strong evidence for practical use of resveratrol in the management of human brain malignancies.

Key words: Resveratrol, glioblastoma, drug metabolism