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*Abstract*

# Synergistic Cytotoxic Effects of Resveratrol in Combination with Ceramide Metabolizing Enzymes in Ph + Acute Lymphoblastic Leukemia †

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**Abstract:** Bioactive sphingolipids are a lipid family including ceramide, sphingosine-1-phosphate (S1P) and glucosyl ceramide (GC). Ceramide produced through *de novo* synthesis pathway (Serine Palmitoyl Transferase (SPT) is a key enzyme subjected to regulation) plays significant roles in the induction of apoptosis. On the other hand, the conversion of ceramide into S1P and GC by sphingosine kinase 1 (SK-1) and glucosyl ceramide synthase (GCS) induce the proliferation of cancer cells. It is aimed to investigate therapeutic potential of resveratrol on Ph + ALL cells and to identify potential mechanisms behind resveratrol-mediated cytotoxicity in association with targeting of ceramide metabolism. The antiproliferative effects of resveratrol, SPT inhibitor (myriocin), SK-1 inhibitor (SKI II), GCS inhibitor (PDMP), resveratrol: SPT inhibitor, resveratrol: SK-1 inhibitor and resveratrol:GCS inhibitor combinations on SD-1 cells are investigated by cell proliferation assay. The combination indexes are calculated using Calcusyn program. There were synergistic cytotoxic effects of resveratrol with co-administration of myriocin, SK-1 inhibitor and GCS inhibitor. This preliminary data showed for the first time that resveratrol might inhibit the growth of Ph + ALL cells through targeting ceramide metabolism. Molecular studies are still undergoing to reveal the mechanisms behind this synergistic effects.

**Keywords:** Ph + ALL; resveratrol; ceramide; serine palmitoyl transferase; sphingosine kinase 1

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