YS-5, A NOVEL NEOLIGNAN INDUCES APOPTOTIC CELL DEATH INVOLVING ACTIVATED SPINDLE ASSEMBLY CHECKPOINT IN HUMAN CANCER CELLS

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ABSTRACT

BACKGROUND and PURPOSE: We previously demonstrated a novel neolignan compound (Salvinal) which possesses potent anti-cancer activity by suppressing microtubule polymerization. To improve the anti-cancer potency of this type of compound, we identified a Salvinal derivative, 7-acetoxy-2-(3,4- diacetoxyphenyl)-5- (2-met hoxycarbonylvinyl)- benzofuran-3-carboxylic acid methyl ester (YS-5) as a most potential lead on extremely potent cytotoxicity. The action of molecular mechanism of YS-5 was evaluated in this study.

METHODS: The in vitro anticancer effect of YS-5 was examined by the methylene blue dye assay. Enzymatic activity assay, tubulin competition-binding scintillation proximity assay, flow cytometry, immunofluorescence and western blot were used to reveal molecular events in this study.

RESULTS: Here we show that YS-5 is potenly effective against KB and its derived drug resistant cells that indicates YS-5 is a poor substrate for transport by P-gp170/MDR and MRP. In contrast with Salvinal in suppressing tubulin assembly, YS-5 causes microtubule bundle formation like Paclitaxel then arrests mitosis by increased cyclin B1 and mobility shift of Cdc25c. Furthermore, the expression level of spindle assembly checkpoints, including p-BubR1, Bub1, and securin were significantly increased in YS-5 treated cells. However, loss of CDC20 expression was noted after YS-5 treatment. Moreover, we found that YS-5 treatment led to marked increase in the numbers of centrosome abnormalities and apoptosis. Finally, in combined with other chemotherapeutic drugs, a strong synergism between YS-5 and vincristine was noted.

CONCLUSIONS: These findings indicate YS-5 is a promising anticancer compound that has potential for management of various malignancies, particularly for patients with drug resistance.