Melatonin Enhances Venetoclax Sensitivity Through Modulation of Apoptotic and Resistance Pathways in Acute Myeloid Leukemia

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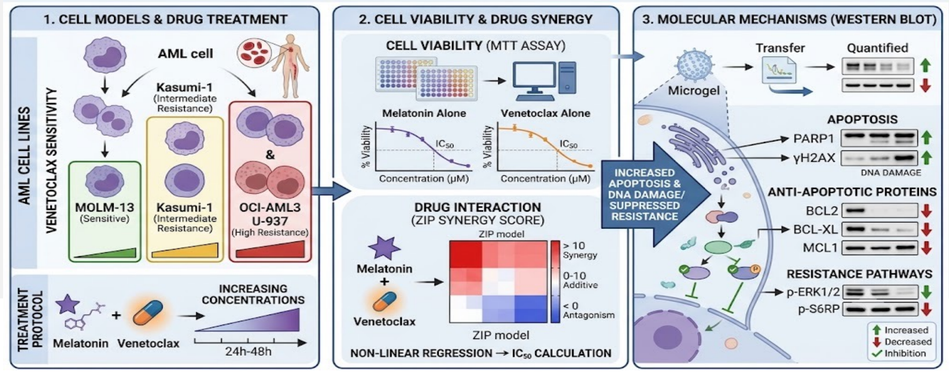
INTRODUCTION

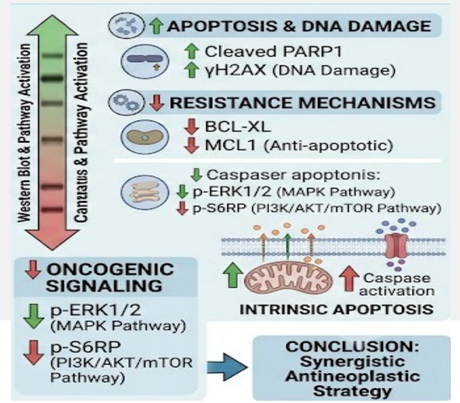
Venetoclax-based therapies have significantly improved outcomes in acute myeloid leukemia (AML) particularly in elderly or unfit patients. However, acquired and intrinsic resistance mediated by antiapoptotic proteins and survival signaling pathways remains a major therapeutic challenge. Melatonin, a pleiotropic indoleamine with experimentally documented antineoplastic and proapoptotic properties, has emerged as a potential novel adjuvant capable of modulating mitochondrial apoptosis and overcoming therapy resistance in AML.

METHOD



CONCLUSIONS

Our findings provide mechanistic evidence supporting melatonin as a multifunctional adjuvant capable of enhancing venetoclax activity and overcoming resistance mechanisms in AML. This combinatorial strategy represents a promising translational approach for improving targeted therapy efficacy in AML and warrants further preclinical and clinical investigation.



RESULTS

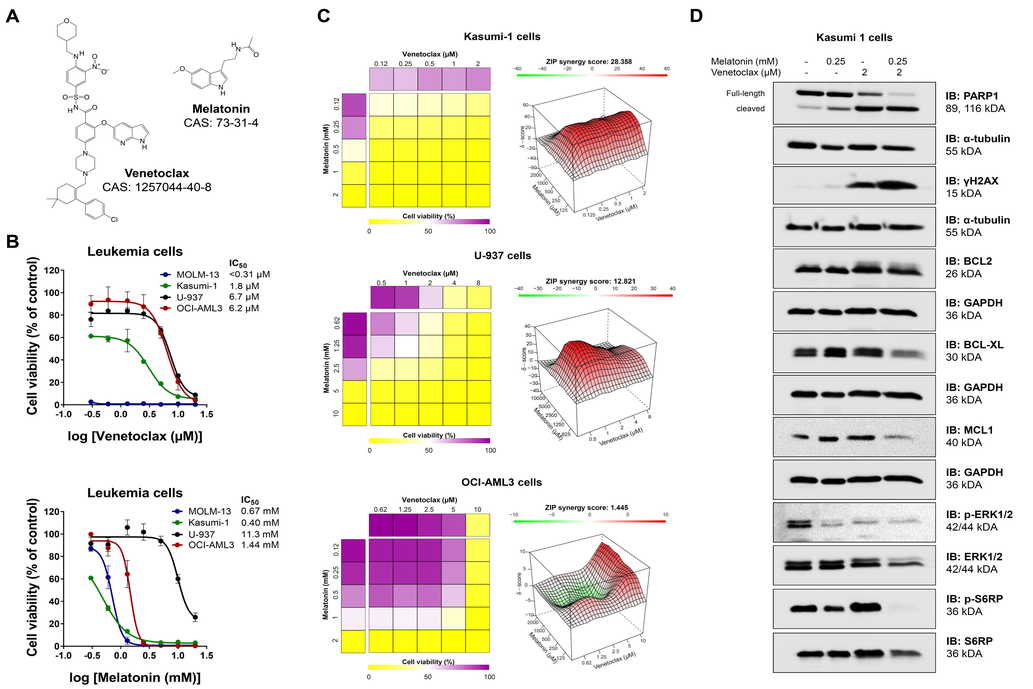


Figure 1. Melatonin enhances venetoclax-induced cytotoxicity in AML cell lines. (A) Chemical structures of venetoclax (CAS: 1257044-40-8) and melatonin (CAS: 73-31-4). (B) Concentration–response cytotoxicity was evaluated using an MTT(3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) tetrazolium assay in a panel of acute myeloid leukemia cell lines treated with vehicle or increasing concentrations of venetoclax or melatonin for 72 h. Values are expressed as the percentage of viable cells relative to vehicle-treated controls. IC50 values and corresponding cell lines are indicated in the figure. (C) Concentration-response cytotoxicity of combination treatments was assessed by MTT assay in Kasumi-1, U-937, and OCI-AML3 cells treated with increasing concentrations of venetoclax and melatonin, either alone or in combination, for 72 h. Cell viability is expressed as a percentage relative to vehicle-treated controls. Results represent the mean of at least three independent experiments. (D) Western blot analysis of total and cleaved PARP1, γH2AX, BCL2, BCL-XL, MCL1, phosphorylated ERK1/2 (p-ERK1/2), total ERK1/2, phosphorylated S6RP (p-S6RP), and total S6RP in whole-cell extracts from Kasumi-1 cells treated with vehicle, venetoclax, and/or melatonin at the indicated concentrations for 72 hours. Membranes were reprobed for α-tubulin or GAPDH as loading controls and developed using Super Signal™ West Dura Extended Duration Substrate with a G:BOX Chemi XX6 imaging system.

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