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653.MULTIPLE MYELOMA: PROSPECTIVE THERAPEUTIC TRIALS

Efficacy Evaluation of a Tetracyclic Triterpene Compound Targeting Multiple Apoptosis Proteins for the Development of a Multiple Myeloma Treatment

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Introduction:Multiple myeloma (MM) is an incurable hematologic cancer that originates in plasma cells and occurs primarily in older patients over 60. This study screened for hit compounds for MM treatments targeting mitochondria and apoptosis proteins. Further, non-clinical testing, including molecular docking analysis, was performed.
Methods: Based on our previous studies, candidate compounds targeting mitochondria were screened (www.medchemexpress.com). The killing effect of the compounds on MM cell lines (RPMI8226, IM9, and U266) was examined using a sulforhodamine B assay. Apoptosis mechanisms were investigated in vitro. Complex immunocompromised mice were established by injecting RPMI8226-RFP-FLuc cells through the tail vein. Efficacy of the KBB-N2 activity was assessed following intraperitoneal (15 or 30 mg/kg/day) and tail vein (7 mg/kg/day) infusions for three days a week at daily intervals. Toxicity, pharmacokinetics, and molecular docking analyses were performed according to the established protocols.
Results: The hit compound, KBB-N2, a tetracyclic triterpene, was identified as an MM-targeted compound with cytotoxic effects. The primary mechanism of action of KBB-N2 in MM cells was inhibiting the activity of the mitochondrial electron transport (ETC) complex, resulting in the generation of excess intracellular reactive oxygen species (ROS), which led to tumor cell death by ROS-mediated apoptosis. In addition, exposure to KBB-N2 inhibited the activity of catalase, a powerful antioxidant enzyme in MM cells. Severe suppression of normal hematopoietic stem cell function was observed with lenalidomide administration at a concentration of 25 μM. However, this toxicity was not observed when KBB-N2 was administered at doses up to 60 μM. KBB-N2 activity involves PARP cleavage and caspase activation in the apoptotic pathway. Furthermore, KBB-N2 inhibited cell growth and exerted cytotoxicity. KBB-N2 induced apoptosis by activating the P53 apoptosis pathway in MM cells. In vivo, all untreated tumor-bearing mice showed rapid tumor growth and severe plasmacytomas, which led to death within seven weeks. Mice treated with KBB-N2 had significantly inhibited tumor growth and longer survival times. The molecular docking assay revealed the optimal docking conformation binding energy of KBB-N2 with docking scores (kcal/M) of -7.3 and -9.8 for ETC complexes I and III, respectively.
Conclusions: The triterpene compound, KBB-N2, was identified as a hit compound and may act as a targeted agent for MM treatment. The antimyeloma activity of KBB-N2 involves interference with the ETC complex and leads to MM cell death.

Disclosures No relevant conflicts of interest to declare.

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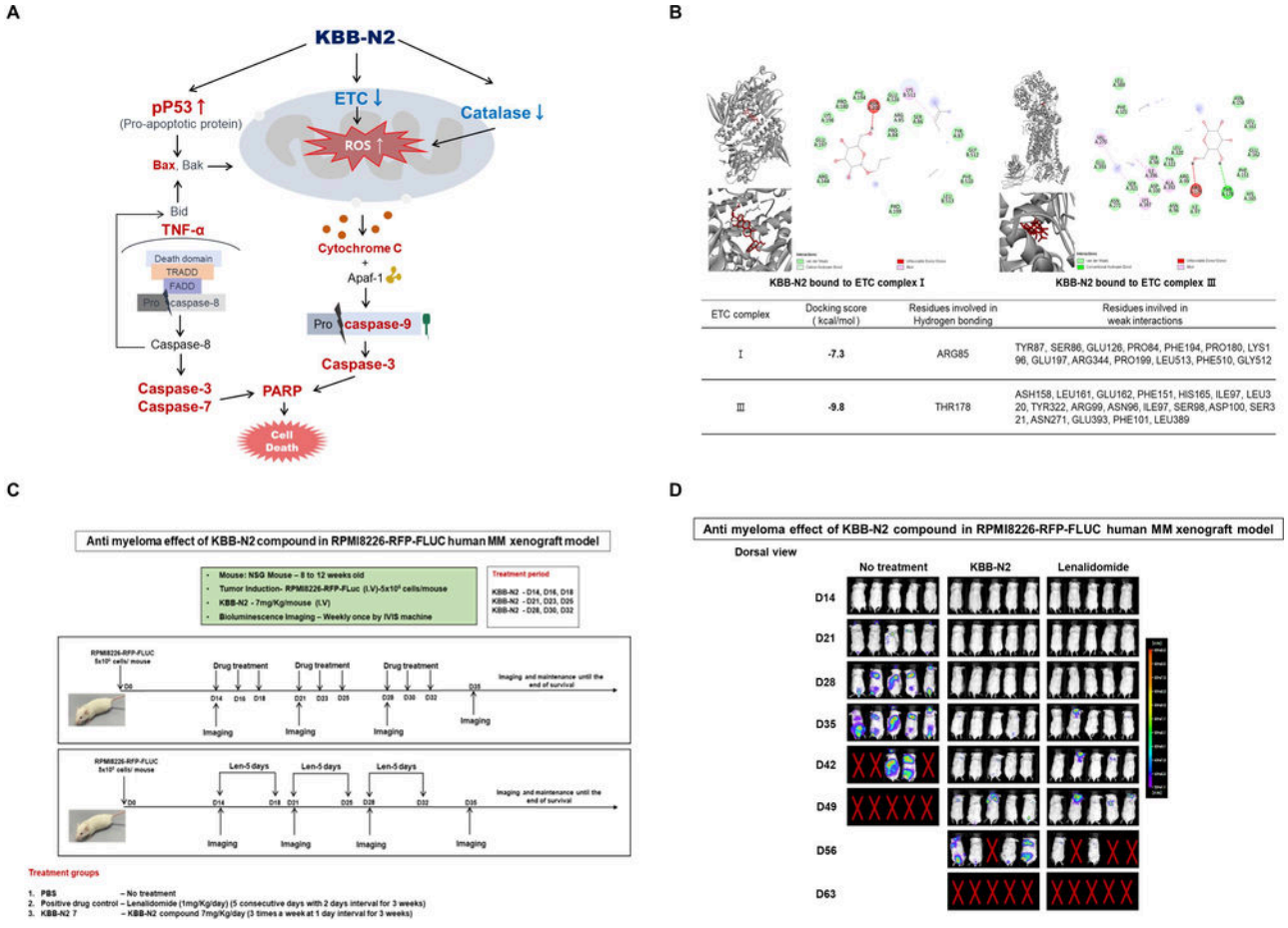

Figure 1

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