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Nephthoquinone derivative PPE8 induces endoplasmic reticulum stress in p53 null H1299 cells

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Endoplasmic reticulum (ER) plays a key role in synthesizing secretory proteins and sensing signal function in eukaryotic cells. Responding to calcium disturbance, oxidation state change, or pharmacological agents, ER transmembrane protein, inositol-regulating enzyme 1 (IRE1) senses the stress and is activated to trigger downstream signals. Glucose-regulated protein 78 (GRP78) dissociates from IRE1 to assist protein folding and guard against cell death. In prolonged ER stress, IRE1 recruits and activates apoptosis signal-regulating kinase 1 (ASK1), as well as downstream JNK for cell death. Naphthoquinones are widespread natural phenolic compounds. Its derivative vitamin K_3 inhibits variant tumor cell growth via alternate oxidation state. We synthesized a novel naphthoquinone derivative PPE8 and evaluated capacity to induce ER stress in p53 null H1299 and p53 wild-type A549 cells. In H1299 cells, PPE8 induced ER enlargement, GRP78 expression, and transient IER1 activation. Activated IRE1 recruited ASK1 for downstream JNK phosphorylation. IRE1 knockdown by siRNA attenuated PPE8-induced JNK phosphorylation and cytotoxicity. Prolonged JNK phosphorylation may be involved in PPE8-induced cytotoxicity. Such results did not arise in A549 cells, but p53 knockdown by siRNA restored PPE8-induced GRP78 expression and JNK phosphorylation. We offer a novel compound to induce ER stress and cytotoxicity in p53-deficient cancer cells, presenting an opportunity for treatment.