Chemoresistance in cancer is a well-known phenomenon that occurs when malignant cells become tolerant to conventional (genotoxic) anticancer therapeutics (cAT). Therefore, overcoming intrinsic or acquired drug resistance is a major challenge in cancer treatment. cAT act cytotoxic through inducing DNA damage. In consequence of DNA damage, a complex stress response, termed DNA damage response (DDR), gets activated. Since the DDR regulates the balance between survival and death, it is assumed that its modulation may overcome anticancer drug resistance of tumor cells. Up to now, several natural compounds (NC) have been identified that modulate the DDR on their own or in combination with the cAT cisplatin (cis) and doxorubicin (doxo). Therefore, the aim of the study is to characterize these identified NC and other candidate compounds regarding their cytotoxic and DDR-modulating potency in cAT-resistant tumor cells of different origin. To identify the therapeutic window, cytotoxic effects on normal cells will be additionally investigated. Finally, the anti-tumor efficacy of the most promising NC will be analyzed in preclinical in vivo studies.