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RESEARCH ARTICLE

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The effects and mechanisms of aloe-emodin on reversing adriamycin-induced resistance of MCF-7/ADR cells

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Multidrug resistance (MDR) is one of the major obstacles for clinical effective chemotherapy. In this study, the effects and possible mechanisms of aloe-emodin (AE) were investigated on reversing the adriamycin (ADR)-induced resistance of MCF-7/ADR cells. AE could significantly reverse the ADR resistance in MCF-7/ADR cells. The combination of AE (20 μM) and ADR had no effect on the P-glycoprotein (P-gp) level, but notably promoted the accumulation of ADR in drug-resistant cells. The efflux function of P-gp required ATP, but AE reduced the intracellular ATP level. AE played a reversal role might through inhibiting the efflux function of P-gp. The research result of energy metabolism pathways indicated that combination of AE and ADR could inhibit glycolysis, tricarboxylic acid (TCA) cycle, glutamine metabolism, and related amino acid synthesis pathways. Moreover, we found AE not only reversed ADR-induced resistant but also induced autophagy as a defense mechanism. In addition, the combination of AE and ADR arrested G2/M cell cycle and induced apoptosis through DNA damage, ROS generation, caspase-3 activation. Our study indicated that AE could be a potential reversal agent to resensitize ADR resistant in tumor chemotherapy and inhibiting autophagy might be an effective strategy to further enhance the reversal activity of AE.

KEYWORDS
adriamycin (ADR), aloe-emodin (AE), breast cancer, energy metabolism, multidrug resistance (MDR), P-glycoprotein (P-gp)

1 | INTRODUCTION

The incidence rate of breast cancer is the highest in female malignant tumors (Siegel, Miller, & Jemal, 2019). Chemotherapy is one of the main means for clinical treatment of breast cancer. However, the emergence of multidrug resistance (MDR) has led to an increase in the failure of clinical chemotherapy (Ke et al., 2018; Tang, Wang, Kiani, & Wang, 2016). MDR refers to the ability of cancer cells to acquire drug resistance after being induced by a certain drug, then produce cross-resistance to a variety of structurally and functionally unrelated chemotherapy drugs (Zhang et al., 2019). The mechanism of MDR is very complex, in which the overexpression of membrane transporter belonging to ATP binding cassette (ABC) transporter superfamily is the main mechanism. Among these transporters, the overexpression of P-glycoprotein (P-gp) is the most classical and intensive studied mechanism (Zinzi et al., 2014). P-gp, encoded by *MDR1* gene, is considered to be an energy-dependent drug efflux pump, which contributes to reduce the content of chemotherapy drugs in cancer cells. Downregulating the expression of P-gp or inhibiting the function of P-gp can block the efflux effect (Li et al., 2019; J. Pan, Miao, & Chen, 2018; Sun et al., 2019). Consequently, it is very meaningful to search a reversal agent targeting P-gp. It can improve the concentration of intracellular chemotherapeutics, thereby achieving the purpose of enhancing chemotherapy.

Over the past few years, many reversal agents targeting P-gp have been found, but none of them have passed the clinical trials due to their serious side effects (Abdallah, Al-Abd, El-Dine, & El-Halawany, 2015). Therefore, it is urgent to develop new compounds

