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The impaired redox balance induced by methyl gallate dictates iron-mediated cell death in breast cancer cells

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Abstract

Natural products constitute a chemically diverse class of compounds, which represent a strategic resource for rational drug design aimed at the development of multi-target therapeutic agents.
In the present work, we investigated the anticancer activity of methyl gallate (MG) on MDA-MB-231 triple-negative breast cancer cells. Our findings indicate that MG reduced cell viability in a dose- and time-dependent fashion promoting an early increase in reactive oxygen species (ROS). Notably, MG cytotoxic effect as well as ROS-mediated cell death was partly rescued by antioxidant N-acetyl-l-cysteine (NAC). This phenomenon was accompanied with the activation of Keap-1/Nrf2 signaling pathway and the upregulation in MnSOD and catalase content.
Interestingly, when cells were pre-treated with ferrostatin-1 (FRS), a recognized inhibitor of ferroptosis, the cytotoxic impact of MG was alleviated, indicating that an iron-dependent cell death could be involved in MG mechanism. This hypothesis was supported by western blot analyses demonstrating that MG decreased both FTH1 and GPX4, two well-known players in ferroptotic process, and such an effect was reversed by either FRS or NAC addition.
MG also caused an increase in intracellular iron levels, loss of mitochondrial membrane potential, increase in lipid peroxidation and GSH depletion, all key driving events in ferroptotic cell demise.
As a whole, our findings reveal that MG triggers a redox imbalance and is able to boost an iron-mediated cell death in breast cancer cells. These insights highlight the potential of natural compounds as complementary agents in the ongoing battle against cancer, thus encouraging research in this field.

Categories

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