



Original article

Effect and mechanism of dihydromyricetin protection against radiation-induced intestinal injury

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ABSTRACT

Objective: To investigate the protective effects of dihydromyricetin (DHM) against radiation-induced intestinal injury (RIII) and its underlying mechanism by both *in vivo* and *in vitro* experiments.

Methods: Sixty male mice were randomly divided into 6 groups: control group, whole-abdominal irradiation (WAI)+0.5% sodium carboxymethyl cellulose (CMCNa) group, WAI + DHM (50 mg/kg) group, WAI + DHM (100 mg/kg) group, WAI + DHM (200 mg/kg) group, and WAI + amifostine (100 mg/kg) group. An animal model of RIII was then established by administering 12 Gy abdominal local irradiation to all groups. The protective effects of DHM was evaluated by hematoxylin and eosin staining (HE), villin staining, and the FITC-dextran method. The *in vitro* radioprotective effects of DHM was further evaluated by colony formation assay. Flow cytometry was used to analyze cell cycle distribution, apoptosis, and reactive oxygen species (ROS) levels. Western blot assay was used to examine the expression of proteins related to apoptosis, ferroptosis, ROS, DNA damage, and autophagy. Additionally, immunofluorescence staining was performed to detect γ -H2AX foci formation as a marker of DNA double-strand breaks. Finally, the effect of DHM on colon cancer radiosensitivity was tested by *in vitro* and *in vivo* colony formation and tumor-bearing experiments.

Results: In the RIII model, DHM showed radioprotective effects by increasing colon length, ameliorating villus injury, promoting crypt cell proliferation, and mitigating mucosal barrier damage ($P < 0.05$). *In vitro* experiment indicated that DHM significantly reduced radiation-induced apoptosis (control: 4.27 ± 0.61 , DHM: 3.46 ± 1.31 , IR: 23.46 ± 0.89 , IR + DHM: 12.47 ± 0.36 , $P < 0.001$), ROS accumulation ($P < 0.05$), and DNA damage ($P < 0.001$). The radioprotective effects of DHM might be closely associated with autophagy regulation and Nrf2 pathway activation. Moreover, DHM showed antitumor activity against colon cancer cells without conferring radioprotective effects on them.

Conclusions: DHM can effectively alleviate RIII indicated by both *in vivo* and *in vitro* experiments, suggesting its potential to be used as a radioprotective agent.

1. Introduction

Radiotherapy is one of the main treatment methods for pelvic and abdominal cancer, and over 50% of pelvic and abdominal cancer

patients receive radiotherapy.¹ However, the intestine is highly sensitive to ionizing radiation,^{2,3} so radiation-induced intestinal injury (RIII) at different levels often occur in patients with pelvic and abdominal cancer after radiotherapy, resulting in the loss of intestinal stem cells and

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