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### Protective effects of hominis placenta hydrolysates on radiation enteropathy in mice

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## SHORT COMMUNICATION

### Protective effects of hominis placenta hydrolysates on radiation enteropathy in mice

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The aim of this study was to investigate whether the hominis placenta hydrolysates (HPhs) have a protective effect against radiation-induced enteropathies. HPh (1–10 mg kg<sup>-1</sup>, i.p.) was treated to C57BL/6 mice, once daily for 5 days. Mice were irradiated (10 Gy) 1 h after the last injection. Cell damage was investigated at 24 and 72 h by haematoxylin-eosin staining, and the apoptotic index was determined at 24 h by deoxynucleotidyl transferase-mediated dUTP nick end labelling staining. The results showed that the HPh alleviated radiation-induced damage of crypts and suppressed apoptosis dose dependently. In conclusion, hominis placenta might be a beneficial agent against radiation-induced intestinal complications.

**Keywords:** hominis placenta hydrolysates; radiation; jejunal crypt; apoptosis; TUNEL

#### 1. Introduction

Enteropathy, as a primary and serious complication, is easily induced by local radiation in the treatment of abdominal and pelvic cancers (Somosy, Horvath, Telbisz, Rez, & Palfia, 2002). Acute radiation injury to the intestinal mucosa has been well-reported to lead to chronic radiation enteritis, possibly impacting the patient's quality of life (Donner, 1998). Thus, radiation-induced enteritis is an important factor for dose limitation in abdominal and pelvic radiotherapy, and it still remains an important obstacle for achieving radiocurability (Paris et al., 2001). Acute radiation toxicity in the intestine seems to be the result of apoptotic crypt cell death, which is one of the most distinctive features and oxidative stress is known to be one of the mechanisms of cell death (Kern & Kehrer, 2005).

Hominis placenta (HP) is a dried placenta isolated from healthy pregnant women after delivery; it has been used to invigorate vital essences and blood in traditional

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medicines in East Asia (Goldfarb, Doan, & Duran, 1980). HP is a rich resource of various bioactive substances such as polydeoxyribonucleotides, ribonucleic acid (RNA), deoxyribonucleic acid (DNA), peptides, amino acids, enzymes and trace elements (Shibasaki, Odagiri, Shizume, & Ling, 1982). It is also known to have various pharmacological effects. Among these effects, anti-oxidative effect is closely related to radiation-induced cell damage. In addition, other axonal regenerative effect and inhibitory effect on myelosuppression may be also related to cell damage. Furthermore, tonic herbs are usually used to prevent or treat radiation-induced body complications (Li et al., 2007). HP is also among the most widely used tonic herbs in traditional medicine. Thus, we hypothesised that HP might have a protective effect against radiation.

In this study, the protective effect of HP against radiation-induced damages and apoptotic changes in intestinal crypt cells was investigated *via* haematoxylin–eosin staining and terminal deoxynucleotidyl transferase-mediated dUTP nick end labelling (TUNEL) staining.

## 2. Results and discussion

Since the crypts of the small intestine are the most sensitive to radiation-induced damage (Somosy et al., 2002), radiation of the intestine could cause acute morphological changes such as shortened villi and reduced thickness of the mucosa, along with malabsorption, diarrhoea, urgency, faecal incontinence and tenesmus (Andreyev, 2005).

Radiation in the range of 5–10 Gy has been reported to destroy crypt cells reversibly in mice; however more than 10 Gy radiation has been known to destroy intestinal crypt cells irreversibly (Farrel, 1994). Thus, 10 Gy radiation was selected as the test radiation in this study.

In this experiment, hominis placenta hydrolysate (HPh) 5 and 10 mg kg<sup>-1</sup> pre-treatment protected the crypt cells against radiation-induced damage by 30.4% and 56.7% at 24 h (38.1 ± 3.2 in the vehicle-treated group *versus* 51.4 ± 4.3, and 62.9 ± 4.0 in 5 and 10 mg kg<sup>-1</sup> HPh pre-treated group). The effects were maintained at 72 h by 38.4% and 52.5% (42.3 ± 2.8 in the vehicle-treated group *versus* 57.9 ± 3.5, and 63.6 ± 3.9 in 5 and 10 mg kg<sup>-1</sup> HPh pre-treated group) (Figure 1 and Supplementary Figure S1 – online only).

Several tonic herbs including ginseng and *Paeonia lactiflora* have been reported to have beneficial effects on radiation-induced complications (Li et al., 2007; Takeda, Katoh, & Yonezawa, 1982). Thus HP as a tonic was postulated to have a similar effect, and previous research on pharmacological effects supports the results of this study (Seo et al., 2006).

Therefore, it could be assumed that HPh might have protective effects against radiation-induced gastrointestinal tract damage and may also relieve the clinical side effects of radiation therapy such as vomiting and diarrhoea.

Another result indicated that HPh had reduced the number of TUNEL-positive cells at 24 h after radiation in a dose-dependent manner. The number of TUNEL-positive cells was 28.0 ± 5.3 (the apoptotic index = 2.8%) in the normal group, 388.0 ± 5.8 (38.8%) in the vehicle-treated group, 302.0 ± 11.5 (30.2%), 208.0 ± 8.6

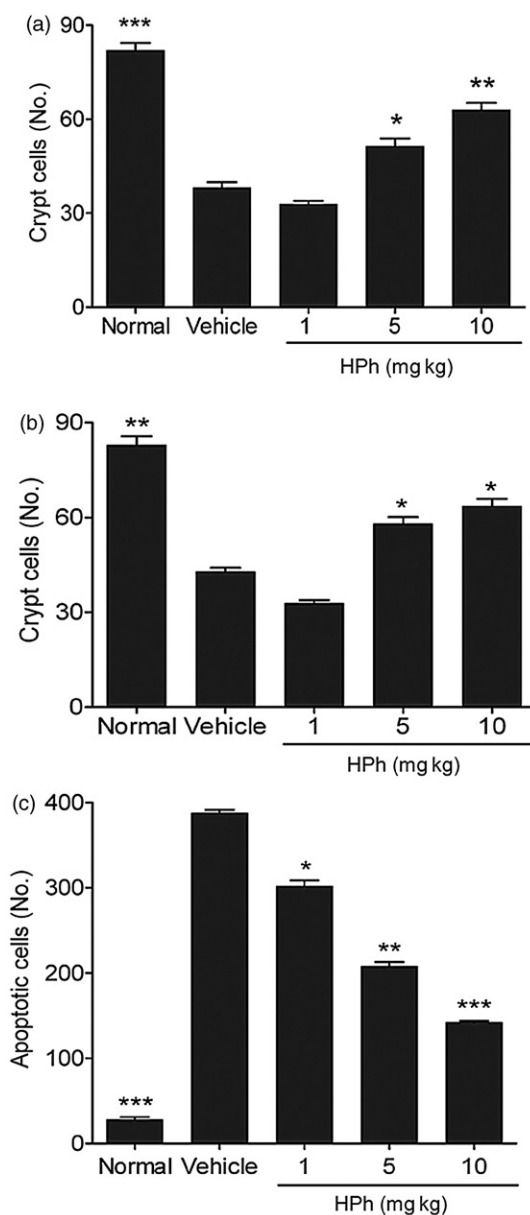


Figure 1. Effect of HPh on the number of small intestinal crypts at 24 (a) and 72 h (b) and apoptosis in small intestinal crypt cells at 24 h (c) after exposure to 10 Gy radiation. Normal means normal group, vehicle means vehicle-treated group and 1, 5 and 10 indicate HPh 1, 5 and 10 mg kg<sup>-1</sup> pre-treated group, respectively. Values are represented as the mean  $\pm$  SE. \* $p$  < 0.05, \*\* $p$  < 0.01, \*\*\* $p$  < 0.001 vs. vehicle-treated group.

(20.8%) and  $142.0 \pm 3.7$  (14.2%) in the HPh 1, 5 and 10 mg kg<sup>-1</sup> pre-treated groups, respectively (Supplementary Figures S1 and S2 – online only).

Many researchers have reported that radiation-induced cell death in the intestine is the direct consequence of apoptosis-induced acute cell death

(Kerr, Wyllie, & Currie, 1972; Raguso, Leverage, & Pichard, 2002). Apoptotic cell damage has been reported to reach peak level at 16–24 h after radiation, and then decrease considerably (Ryu, Chung, Kay, Kim, & Yoon, 2001). Thus, in this study, a TUNEL assay was performed 24 h after radiation, and HPh showed a protective effect against radiation-induced apoptosis (50% and 68.3% with doses of 5 and 10 mg kg<sup>-1</sup>, respectively). Therefore, the protective effect of HPh might involve anti-apoptotic effects. Generally, radiation-induced cytotoxicity is known to be, in part, due to overproduction of the reactive oxygen species (ROS) and subsequent apoptotic cell death (Kern & Kehrer, 2005). Although the pathological mechanisms have not been investigated in this study, it can be suggested that these ROS-related mechanisms might be involved in the effect of HPh, because HP is known to have antioxidative effects (Avissar et al., 1994; Togashi et al., 2002). HP contains antioxidant collagen peptides (e.g. uracil, tyrosine, phenylalanine and tryptophan; Togashi et al., 2002) and involves a defense mechanism such as glutathione peroxidase that protects the embryo against oxidative stress (Avissar et al., 1994; Togashi et al., 2002).

### 3. Conclusion

HPh showed a preventive effect against radiation-induced apoptosis in mice jejunal crypt cells and thus could be beneficial against radiation-induced intestinal complications. However, further studies on various target mechanisms, including the anti-oxidation of HPh, should be conducted.

### Supplementary material

Experimental details relating to this paper are available online, alongside Figures S1 and S2.

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