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The effects of Teucrium polium on ionizing radiation-induced intestinal damage in rats

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Abstract

Background and study aims : **Oxidative stress plays an important role in development of intestinal injury after abdomino-pelvic radiation therapy. *Teucrium polium* (TP) is a medicinal plant which has antioxidant and anti-inflammatory properties. The aim of this study was to investigate the effect of TP on radiation-induced intestinal oxidative damage in rats.**

Materials and methods : **Group 1 (n = 8), the control group ; Group 2 (n = 8), the RAD (radiation) group in which each rat received a single whole-body 800 cGy radiation performed with a LINAC ; Group 3 (n = 8), the RAD + TP group in which rats were exposed to radiation as in Group 2, followed by intragastric administration of 0.5 g/kg/daily TP extract for 7 consecutive days ; and Group 4 (n = 8), the TP group, rats received only intragastric TP for 7 days.**

Results : **Radiation led to intestinal damage, which was accompanied by an increase in intestinal thiobarbituric-acid-reactive substances (TBARS) and myeloperoxidase (MPO) levels, and a decrease in reduced glutathione (GSH) levels. Although TP significantly decreased intestinal MPO levels and inflammation scores, it neither reverted intestinal TBARS and GSH levels nor ameliorated other histological parameters of the disease.**

Conclusions : **Our results suggest that TP reduces inflammation but does not ameliorate the increased oxidative stress conditions in radiation-induced intestinal damage in rats.** (Acta gastroenterol. belg., **2011**, 74, **491-496**).

Key words : Teucrium polium, radiation, intestine, oxidative stress, inflammation.

Introduction

Radiation-induced acute intestinal injury after abdominal and pelvic irradiation is a common and serious problem (1-4). Exposure to radiation causes damage to DNA, protein, and lipids in mammalian cells, as well as increased mitochondria-dependent generation of reactive oxygen species (ROS), with subsequent cell cycle checkpoint arrest, apoptosis, and stress-related responses (5). Based on these reports, it is anticipated that antioxidants, through the scavenging of ROS, may attenuate this complication.

The *Teucrium polium* (TP [*Lamiaceae*]) is a wild-growing flowering plant, found abundantly in South-Western Asia, Europe, and North Africa and has approximately 220 genera, and almost 4000 species worldwide. The TP species were used as medical herb for more than 2000 years (6). TP has antioxidant (7), anti-inflammatory, antibacterial, and antipyretic properties (8-11). It has been reported that TP prevents steatohepatitis (12), carbon tetrachloride-induced hepatic injury (13), and gastric ulcers (6) in rats with its ROS scavenging activity. Therefore, we investigated the effect of TP extract on radiation-induced intestinal oxidative damage in rats.

Materials and Methods

Animals

Healthy male Sprague-Dawley rats weighing 250-300 g were used in this study. Animals were housed on a 12-hour light/dark cycle (lights on from 08:00 hours) at a constant ambient temperature (24 ± 1 °C), with normal rat chow and water available ad libitum. The study protocol was in accordance with the guidelines for animal research and was approved by the Ethics Committee of our hospital.

Preparation of the TP extract

The powdered plant material (200 g) was extracted three times with a mixture of ethanol and H_2O (70:30) at room temperature overnight. The accumulated extract was concentrated under reduced pressure on a rotary evaporator to a volume of 200 ml. The concentrated extract was then subjected to in-sequence reextraction with diethyl ether and diethyl acetate, each four times. Each extract was then concentrated under reduced pressure (12,14). The the ethyl acetate extract was used in this study.

Experimental design

Thirty-two male Sprague-Dawley rats were divided into four groups. Group 1 (n = 8), the control group, received no irradiation or treatment. In group 2 (n = 8), the RAD (radiation) group, the rats were exposed to

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radiation performed with a LINAC producing 6 MV photons at a focus 100 cm distant from the skin. Under ketamine anaesthesia (100 mg/kg i.p.), each rat received a single whole-body X-ray irradiation of 800 cGy (15). Animals were returned to their home cages following irradiation. In group 3 (n = 8), the RAD + TP (radiation plus *Teucrium polium*) group, rats were exposed to radiation as described for group 2. On the same day as radiation exposure, the ethyl acetate extract of TP, which was prepared as described previously (12), was administered intragastrically (at 0.5 g/kg/daily) (12) for 7 consecutive days. In group 4 (n = 8), the TP group, rats received only intragastric the ethyl acetate extract of TP (at 0.5 g/kg daily) for 7 consecutive days.

Tissue samples

On day 8 of the study, a laparotomy was performed under sterile conditions after the rats had been anesthetized with 50 mg/kg ketamine (Ketolar ; Parke-Davis, Spain) and 10 mg/kg xylazine HCl (Alfazyne 2% ; Alfasan, The Netherlands). After the skin had been sterilized with iodine and shaved, the abdomen was opened widely. The ileum was excised for histopathological and biochemical analyses including measurement of thiobarbituric-acid-reactive substances (TBARS), reduced glutathione (GSH), and myeloperoxidase (MPO) levels.

Intestine histology

The ileum samples taken from the rats were fixed for 24 h in 5% neutral formol solution. Samples were divided into pieces of 0.5 × 0.5 × 0.5 cm^3 and were processed for routine examination. These samples from each animal were obtained in separate blocks. Sections of samples were cut at 6-7 µm, mounted on slides, stained with hematoxylin and eosin (H&E) and examined by a Leica DFC280 light microscope and Leica Q Win Image Analyses System (Leica Microsystems Imaging Solutions, Cambridge, UK). The tissue slices were scanned and scored by two expert pathologists, who were unaware of the sample assignment to an experimental group. A scoring system ranging from 0 to 3 (0, normal ; 1, mild ; 2, moderate ; 3, severe) was used for intestinal histopathological evaluations. Mucosal integrity, edema, inflammatory cellular infiltration of the lamina propria, and vessel vasodilation were scored accordingly (16).

Biochemical analyses

Preparation of tissue homogenates

Intestinal tissues were removed from the rats and washed three times with cold physiological saline, and the wet weight was recorded. The tissues were sliced into approximately 0.5-1 g portions using a lancet, placed in covered plastic cups wrapped with aluminum foil, and stored at -20 °C until analysis. Tissue samples taken from the freezer on the day of analysis were weighed after they had been thawed at an ambient temperature and then homogenized in a glass–teflon homogenizer (Tempest Virtishear, model 278069 ; Virtis, Gardiner, New York, USA) at 5000 rev/min for 2 min after the addition of 10 volumes of cold KCL (150 mM). The homogenates were used for TBARS analysis on the same day.

Determination of lipid peroxidation

TBARS and other products of lipid peroxidation considered to be indicators of oxidative stress were analyzed using the method described by Buege and Aust (17). Briefly, 250 µL of tissue homogenate, 500 µL of thiobarbituric acid (TBA) reactant (3.7 g/L TBA dissolved in 0.25 mol/L HCl), and 1.5 mL of 15% trichloroacetic acid were added to screw-topped Pyrex centrifuge tubes (~10 mL) and mixed. The tubes were placed in a hot water bath at 95 °C for 30 min and then immediately cooled under tap water. *n*-Butanol (3 mL) was added to each tube and mixed so that the pink chromogen separated into the butanol phase. The absorbance of the colored organic phase was read against a blank at 535 nm. 1,1,3,3-Tetramethoxypropane was used to prepare a calibration curve from which the serum and tissue levels of TBARS were calculated. Tissue levels were expressed as nmol/g wet tissue.

GSH assay

GSH was measured in the tissue homogenates using the method described by Ellman (18). 250 mL of 10% trichloroacetic acid was added to 250 mL of tissue homogenate containing 6 mM disodium EDTA. The mixture was vortexed vigorously for 2 min, followed by centrifugation at 3000 × *g* for 10 min. An aliquot (0.2 mL) of the supernatant was mixed with 1.7 mL of 0.1 M potassium phosphate buffer (pH 7.5), and 0.1 mL of 1 mM Ellman's reagent (5,5´-dithio-bis-[2-nitrobenzoic acid]) was added to each tube. After a 5 min incubation at room temperature, the optical density was measured spectrophotometrically at 412 nm against a reagent blank. The results were expressed as mmol/g wet tissue.

Determination of MPO activity

Tissue samples from the intestine, previously prepared and stored at -20 °C, were thawed, weighed, suspended (10% w/v) in 50 mM potassium phosphate buffer (pH 6.0) containing 0.5% hexadecyltrimethylammonium bromide, and homogenized. The homogenate was sonicated three times for 10 s (Bandelin Electronic, Sonopuls GM 750, Berlin, Germany). After sonication, the specimens were freeze–thawed three times and microcentrifuged at 14,000 × *g* for 15 min at 4 °C. The supernatants were used for MPO analysis.

The MPO assay was performed as follows : 0.1 mL of tissue material was mixed with 2.9 mL of 50 mM

phosphate buffer (pH 6.0) containing 0.167 mg/mL *o*-dianisidine dihydrochloride and 0.0005% hydrogen peroxide (19). The reaction was carried out at room temperature for 5 min. The absorbance change at 460 nm was recorded kinetically with an LKB-UV spectrophotometer (LKB Biochrom Ultraspec Plus, Cambridge, England) at 1 min intervals. One unit of MPO activity was defined as that required to degrade 1 µmol of peroxide per minute at 25 °C. Protein concentrations in the supernatants were measured using Bradford's method (20). MPO activity was expressed as units/g protein.

Statistical analyses

Results are expressed as means ± SD. Comparisons of quantitative variables among the groups were made with one-way analysis of variance or the corresponding nonparametric test (Kruskal–Wallis), as required. For all comparisons, a statistically significant difference was defined as $p < 0.05$.

Results

Effects of TP extract on oxidative stress

Intestinal TBARS and MPO levels in the RAD group were significantly higher than in the control ($p < 0.01$) and TP groups ($p < 0.05$) (Table 1). Intestinal MPO activity in the RAD + TP group was significantly lower than in the RAD group ($p < 0.01$). Intestinal GSH levels in the RAD group were lower than in the control ($p < 0.01$) and TP groups ($p < 0.05$). There was no significant difference between the RAD and RAD + TP groups for intestinal GSH and TBARS levels.

Histopathological results

There was no significant difference between the groups for mucosal integrity. Edema, inflammatory cellular infiltration of the lamina propria and vasodilation scores in the RAD group were significantly higher than in the control group ($p < 0.05$, $p < 0.05$ and $p < 0.01$, respectively) (Table 2) (Fig. 1a and 1b). Inflammatory cellular infiltration of the lamina propria scores in the RAD + TP group were significantly lower than in the RAD group ($p < 0.01$) (Fig. 1c), but there was no significant difference between the RAD + TP and RAD groups for other scores. Inflammatory cellular infiltration of the lamina propria and vasodilation scores in the RAD group were significantly higher than in the TP group ($p < 0.05$ and $p < 0.01$, respectively) (Table 2) (Fig. 1d).

Discussion

In this study, intestinal damage was successfully generated by a single dose whole-body irradiation (800 cGy). This damage was accompanied by increased intestinal TBARS and MPO levels, and decreased GSH levels. Although TP treatment significantly decreased intestinal MPO levels and inflammation scores, it neither reverted intestinal TBARS and GSH levels nor ameliorated other histological parameters of the disease.

Radiation treatment is an important therapeutic option in the management of many tumors. Normal healthy tissues are also commonly affected by this treatment option. The small intestine is considered to be one of the most sensitive organs to radiation therapy (21,22). Nausea, vomiting, and diarrhea are frequently occurring and challenging clinical symptoms following abdominal and pelvic radiation treatments (22). Radiation damage is caused by the overproduction of ROS, including the superoxide anion, hydroxyl radical, and hydrogen peroxide. In our study, intestinal TBARS and MPO levels in the RAD group were significantly higher than in the control group. Also, intestinal GSH levels in the RAD group were lower than in the control group. Intestinal damage scores in the RAD group were significantly higher than in the control group. These findings support the hypothesis that radiation causes intestinal oxidative damage by the overproduction of ROS.

Table 1. — **Comparison of intestinal thiobarbituric acid-reactive substances (iTBARS), reduced glutathione (iGSH), and myeloperoxidase (iMPO) levels between the groups**

Groups	iTBARS (nmol/g wet tissue)	iGSH (mmol/g wet tissue)	iMPO (units/g protein)
Control (n = 8)	0.28 ± 0.01	35 ± 16	15 ± 2
RAD (n = 8)	0.35 ± 0.05*,**	14 ± 2*,***	55 ± 20*,**
RAD + TP (n = 8)	0.35 ± 0.08	14 ± 3	21 ± 11***
TP (n = 8)	0.28 ± 0.03	34 ± 6	16 ± 4

RAD, Radiation ; RAD + TP, Radiation + *Teucrium polium* ; TP : *Teucrium polium*.
Values are given as Mean ± SD.
* $p < 0.01$ compared with the control group.
** $p < 0.05$ compared with the TP group.
*** $p < 0.01$ compared with the RAD group.

Table 2. — **Comparison of intestinal mucosal integrity, edema, inflammatory cellular infiltration of the lamina propria, and vasodilation scores between the groups**

Groups	Intestinal histological parameters			
	MI	Edema	INF	V
Control (n = 8)	0.00 ± 0.00	0.29 ± 0.48	0.86 ± 0.90	0.86 ± 0.69
RAD (n = 8)	0.29 ± 0.75	1.14 ± 0.69*	2.43 ± 0.78*	2.43 ± 0.53**
RAD + TP (n = 8)	0.29 ± 0.75	1.00 ± 0.00	1.14 ± 0.37***	2.00 ± 0.57
TP (n = 8)	0.00 ± 0.00	0.28 ± 0.42	0.43 ± 0.53	0.57 ± 0.53

RAD, Radiation ; RAD + TP, Radiation + *Teucrium polium* ; TP, *Teucrium polium* ; MI, Mucosal integrity ; INF, Inflammatory cellular infiltration of the lamina propria ; V, Vasodilation.
Values are given as Mean ± SD.
* $p < 0.05$ compared with the control and TP groups.
** $p < 0.01$ compared with the control and TP groups.
*** $p < 0.01$ compared with the RAD group.

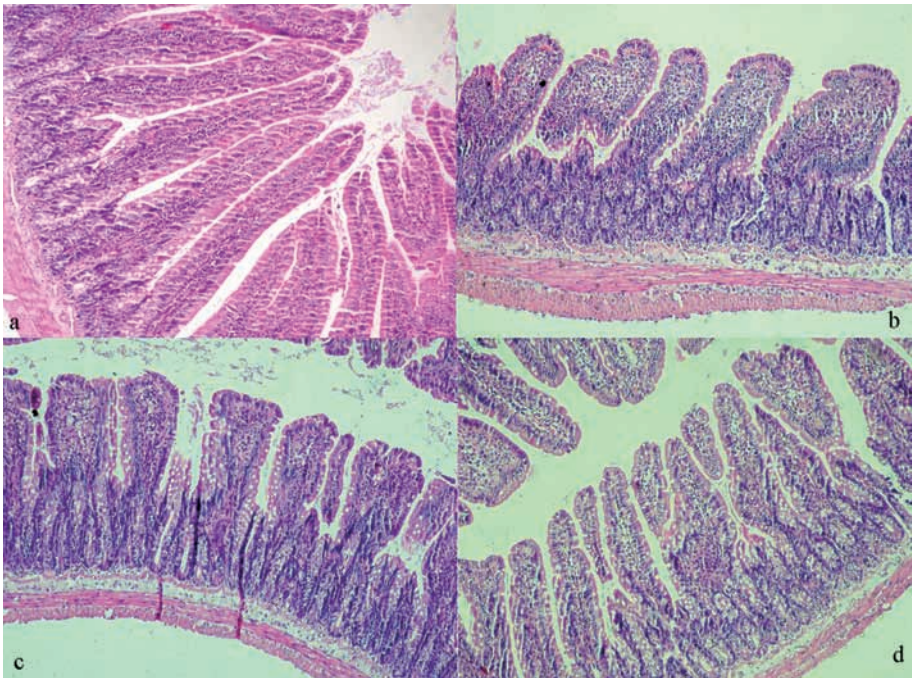

Fig. 1. — Intestinal histology of the control animals (a), the RAD group, (b), the RAD + TP group (c), the TP group (d) (Hematoxylin and eosin, 100 ×). Figure 1b shows radiation-induced histopathological changes (severe edema, inflammation and vasodilation). Figure 1c demonstrates that TP reduces inflammation.

In recent years, many studies have been designed to prevent radiation-induced damage to normal tissue. These studies contain both technological improvements in radiation application and chemical modifiers of radiation damage (23). For this purpose, many antioxidants that scavenge or inhibit the formation of ROS have been investigated in radiation damaged models. Berbée *et al.* reported that gamma-Tocotrienol (an analog of vitamin E) ameliorated radiation-induced intestinal oxidative damage (24). Guney *et al.* reported that melatonin prevented intestinal oxidative damage developed after irradiation exposure in rats (25). It has also been reported that selenium plus vitamin E pretreatment has protective effects against radiation-induced intestinal oxidative damage through their antioxidant activities as well as the modulating activities of some antioxidant enzymes such as superoxide dismutase, catalase, and glutathione peroxidase (26). Although TP has potent antioxidant activity comparable to that of alpha-tocopherol (27), it did not prevent radiation-induced intestinal oxidative damage in our study. It has been shown that TP prevents oxidative damage in the liver (12,13), stomach (6), and pancreas (28). However, to date, no studies have examined the effects of TP on radiation-induced oxidative intestinal damage. Unlike general oxidative stress conditions, it has been suggested that secondary reactive species are generated by hydroxyl radicals in radiation-induced oxidative stress

conditions. These new secondary radical species are blamed for critical target (i.e. DNA) damage. Other important characteristics of these secondary reactive species are that they are less reactive and have different kinetic reactivity. Thus, conventional antioxidants such as vitamin C and vitamin E may not effectively scavenge these products. These secondary radicals can only be scavenged effectively by radioprotectors such as amifostine and nitroxide (23). While many antioxidants have useful effects on radiation-induced intestinal injury, only a few substances have been approved for clinical use in radiation-induced tissue damage. Although it has been reported that TP scavenges hydroxyl radicals effectively in vitro (10), our results suggest that TP does not effectively scavenge secondary radical species in vivo since we show that TP does not ameliorate intestinal oxidative damage in our model.

It is well-known that TP has diuretic, antipyretic, diaphoretic, antispasmodic, tonic, antihypertensive, analgesic, anorexic, antibacterial, and antidiabetic properties (7-9). TP is traditionally used for its anti-inflammatory effects in the treatment of many inflammatory illnesses such as arthritis, eczema, and urinary tract inflammations (29). The anti-inflammatory activity of TP is reported as strong as that of indomethacin (30). It has been suggested that the presence of flavonoids and sterols might be responsible for its potent anti-inflammatory activity (30,31). Mehrabani *et al.* reported that TP significantly decreased gastric mucosal inflammation accompanied by gastric mucosal healing in an indomethacin-induced gastric ulcer model in rats (6). In addition, potent anti-inflammatory effects of TP have been determined in methionine/choline-deficient diet-induced steatohepatitis models (12,32). Similar to the studies described above, we also demonstrated that TP treatment significantly decreased intestinal MPO levels and inflammation scores in radiation-induced intestinal damage in rats (Fig. 1c). Our findings suggest that TP is a plant that possesses potent anti-inflammatory properties.

A single whole-body X-ray irradiation of 800 cGy may also affect the immune system like intestine. We did not evaluate the effects of radiation on the immune system in the present study. However, our results revealed apparent intestinal inflammatory cell infiltration in the RAD group. This finding suggests that radiation does not considerably affect the immune system.

In conclusion, a single dose whole-body radiation causes intestinal oxidative damage in rats. Although administration of TP after radiation exposure reduced inflammation in our model, it did not prevent increased oxidative stress-induced intestinal damage.

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