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Quercetin Prevents Hydrogen Peroxide-induced Necrotic and Apoptotic Cell Death in Human Colonic Epithelial Cells

Soon-Hee Jung

Department of Clinical Pathology, Jinju Health College, Jinju 660-757, Korea

Quercetin is one of the most distributed flavonoids in the plant kingdom and occurs naturally in a wide range of fruits and vegetables. This study was undertaken to determine whether quercetin exerts beneficial effect against necrotic and apoptotic cell death induced by hydrogen peroxide (H_2O2) in intestinal cells using the human-derived cultured T84 colonic epithelial cell line. Necrotic cell death was induced by exposing cells to 0.5 mM H_2O_2 for 2 h and apoptosis was induced by incubating cells in normal culture medium for 18 h following exposure of cells to 0.5 mM H2O2 for 2 h. Cell viability was evaluated by the trypan blue exclusion assay and apoptosis was assessed by Hoechst 33258 staining and flow cytometry. H_2O_2 induced necrotic cell death in a time and dose-dependent fashion. Both necrotic and apoptotic cell deaths were not prevented by the antioxidants N,N'-diphenyl-p-phenylenediamine(DPPD) and Trolox, whereas both cell deaths induced by the organic hydroperoxide t-butylhydroperoxide (tBHP) were prevented by DPPD, suggesting that H_2O_2 induces cell death through a lipid peroxidation-independent mechanism. H2O2-induced necrotic death was prevented by deferoxamine and 3-aminobenzamide, while the apoptotic cell death was not affected by these agents. Quercetin prevented both necrotic and apoptotic cell deaths induced by H_2O_2 in a dose-dependent manner. H_2O_2 caused activation of poly (ADP-ribose) polmerase (PARP), which was inhibited by deferoxamine, 3-aminobenzamide, and quercetin, but not DPPD. These results indicate that quercetin inhibits both necroticand apoptotic deaths of T84 cells. The anti-necrotic effect of quercetin may be attributed to its iron chelator activity rather than a direct H_2O_2 scavenging capacity and antioxidant. The present study suggests that quercetin may play a therapeutic role in the treatment of human gastrointestinal diseases mediated by oxidants.

Key Words : Quercetin, Apoptotic cell, Hydrogen peroxide, Colonic epithelial cell

INTRODUCTION

Reactive oxygen species (ROS) have been implicated in the pathogenesis of gastrointestinal injury in various pathological conditions such as ischemia-reperfusion injury (Kvietys *et al,* 1988), Certain types of drug-induced gastroenteropathy (Vaananen *et al,* 1991), experimental colitis (Keshavarzian *et al,* 1990). and inflammatory bowel diseases (Pavlick *et al,* 2002). Therefore, supplementation of patients with antioxidants may exert beneficial effects in inflammatory bowel disease, at least in part, by antioxidant mechanisms (Simmonds and Rampton, 1993; Pavlick *et al,* 2002).

Flavonoids are phenolic compounds widely distributed in almost every plants and act as pharmacological active constituents in many herbal medicines. They have multiple biological, pharmacological and medicinal properties including anti-inflammatory, anti-allergic, antiviral, anti-

Corresponding Author : Jung, Soon-Hee. Department of Clinical Pathology, Jinju Health College, Jinju 660-757, Korea.
Tel: 010-3584-1847 E-mail: jungsh740@hanmail.net

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thrombotic, antimutagenic, antineoplastic, and hepatoprotective effects (Formica and Regelson, 1995). Quercetin is an important member of the flavonoid family and is found in various food products including fruits, vegetables, olive oil, red wine, and tea. Quercetin exerts a beneficial effect against oxidative damage induced by iron (Nunez *et al,* 2001). and chemicals (Sanchez de Medina *et al,* 2002). and may have anticancer activity (Lipkin *et al,* 1999). in the intestine.

Although the cytoprotective effects of flavonoids such as quercetin have been considered to be associated with their antioxidant activities, it is unclear whether the inhibition of lipid peroxidation is attributed to either a direct interruption of membrane lipid peroxidation or ROS scavenging capacity and iron chelating properties. Earlier studies have shown that the cytoprotection has been related to iron chelating properties (Morel *et al,* 1993; Kostyuk and Potapovich, 1998). and free radical scavenging capacity (Fraga *et al,* 1987; Ratty and Das, 1988). However, other studies have reported that the protective effects of quercetin against oxidant-induced cell injury are due to inhibition of membrane lipid peroxidation by incorporatinginto the membrane lipid bilayer rather than to intracellular scavenging of ROS (Kuhlmann *et al,* 1998; Ahlenstiel *et al,* 2003).

Cell death is classified as necrosis or apoptosis on the basis of established morphological criteria (Cohen *et al,* 1992). Necrosis is considered a passive event in which the cell is irreversibly damaged by an environmental insult, leading to cell death. In contrast, apoptosis is an active process in which the cell itself initiates the molecular machinery to trigger cell death in response to either a physiological stimulus or an environmental stress (Cohen *et al,* 1992). It has been known that oxidants induce cell death through necrosis and apoptosis (Janssen *et al,* 1997; Samali *et al,* 1999). The mode of cell death has been highly variable, depending on the cell type, the nature of the toxin, and the strength and duration of the toxic insult (Raffray and Cohen, 1997). Therefore, the protective effect of agents against oxidant-induced cell injury could be different between two processes (Filipovic *et al,* 1999). Although quercetin has been reported to inhibit oxidant-induced apoptosis (Yokoo and Kitamura, 1997; Ishikawa and Kitamura, 2000). whether this effect is due to antioxidant activity is not clear.

This study was undertaken to examine the effect of quercetin on hydrogen peroxide (H_2O_2)-induced necrotic and apoptotic cell death in intestinal cells using the human-derived cultured colonic epithelial cell line T84. Since it has been shown that the H_2O_2 induces cell injury through a lipid peroxidation-independent mechanism in various cell types (Zager and Burkhart, 1998; Min *et al,* 2000; Park *et al,* 2003). we used H_2O_2 as an oxidant model to determine whether the protective effect of quercetin is due to a direct interruption of membrane lipid peroxidation or radical scavenging activity. If the cytoprotective effect is attributed only to a direct inhibition of membrane lipid peroxidation, quercetin could not prevent the H_2O_2-induced cell death.

MATERIALS AND METHODS Chemicals

[^{3}H]NAD was obtained from Amersham international (Amersham, UK). Hydrogen peroxide (H_2O_2), t-butylhydroeproxide (tBHP), quercetin, deferoxamine (DFO), catalase, (DPPD), Trolox, propidium iodide, and 3-aminobenzamide (3-AB) were purchased from Sigma-Aldrich Chemical (St. Louis, MO, USA). TWEEN 20 was purchased from Calbiochem (California, USA). Antibodies of phospho-ERK and β-actin were obtained from Cell Signaling Technology Inc. (Beverly, MA, USA). All other chemicals were of the highest commercial grade available.

1. Culture of T84 cells

T84 cells were obtained from the American Type Cul-

ture Collection (Rockville, MD) and maintained by serial passages in 75 cm^2 culture flasks (Costar, Cambridge, MA). The cells were grown as monolayer cultures in Dulbecco's modified Eagle's medium/Ham's F12 (DMEM/F12, Sigma Chemical Co.) containing 10% fetal bovine serum at 37℃ in 95% air/5% CO_2 incubator.

2. Induction of necrotic and apoptotic cell death

For induction of necrotic cell death, cells were exposed to 1.0 mM H_2O_2 or tBHP in Hanks' balanced salt solution (HBSS, Sigma Co, USA) for 2 hrs, and apoptotic cell death was induced by incubating cells for a further 18 hrs in normal culture medium following exposure of cells to 0.5 mM H_2O_2 or 0.3 mM tBHP in HBSS for 2 hrs. In experiments to examine effects of inhibitors, test agents were added to medium during exposure of cells to oxidants.

3. Measurement of cell viability

Cell viability was determined bya trypan blue exclusion assay. The cells were harvested using 0.025% trypsin, incubated with 4% trypan blue solution, and were counted using a hemocytometer under light microscopy. Cells failing to exclude the dye were considered nonviable, and the data were expressed as a percentage of viable cells to total cells.

4. Measurement of apoptotic cells

To estimate whether cell death was attributed to necrosis or apoptosis, cells were stained with the fluorescent dye Hoechst 33258. Cells were grown on 22 mm glass coverslips in 6-well plates. After treatment with oxidants, the cells were washed twice with PBS and fixed with 4% paraformaldehyde in PBS (pH 7.4) for 1 hr at 4℃. The fixed cells were washed twice with PBS and stained with 10 μM Hoechst 33258 for 15 min at 37℃. Then cells were washed twice with PBS and examined by confocal microscopy (LSM510, ZEISS, Germany). Apoptotic cells were identified by condensation and fragmentation of nuclei.

Apoptosis was quantified by fluorescence-activated cell sorter (FACS) analysis (Ormerod *et al,* 1992). Cells were grown in six well plates and were treated as indicated. Then, attached and floating cells were pooled, pelleted by centrifugation, washed in phosphate-buffered saline, and fixed with cold 70% ethanol containing 0.5% tween 20 at 4℃ overnight. Cells were washed, resuspended in 1.0 mL of propidium iodide solution containing 100 μg of RNase A/mL and 50 μg propidium iodide/mL. Cells were incubated for 30 min at 37℃ and analyzed. Cells with sub-G1 propidium iodide incorporation were considered as apoptotic. The percentage of apoptotic cells was calculated as the ratio of events on sub-G_1 to events from the whole population.

5. Measurement of poly (ADP-ribose) polmerase (PARP) activity

Cells were treated with H_2O_2 and preincubated for 10 min in a buffer containing 28 mM NaCl, 28 mM KCl, 2 mM $MgCl_2$, 56 mM Hepes (pH 7.5), 0.01% digitonin, and 125 mM NAD (containing 0.25 μCi [^{3}H]NAD). Permeabilized cells were incubated for 5 min at 37℃, and the protein ribosylated with [^{3}H]NAD was precipitated with 200 μL of 50% (w/v) trichloroacetic acid. After washing twice with trichloroacetic acid, the protein pellet was solubilized with 200 μL of 2% (w/v) sodium dodecyl sulfate in 0.1 M NaOH and incubated at 37℃ overnight, and the radioactivity was determined by scintillation counting.

6. Statistical analysis

The data are expressed as mean±SE and the difference between two groups was evaluated using Student's t-test. Multiple group comparison was done using one-way analysis of variance followed by the Tukey post hoc test. A probability level of 0.05 was used to establish significance.

RESULTS

1. Induction of necrotic and apoptotic cell death

Many cells exhibit bimodal responses, with necrotic cell death and apoptotic cell death. Necrosis is a rapid response, while apoptosis is a slow response (Eastman, 1993; Lieberthal *et al,* 1996). In order to evaluate the effect of quercetin on necrotic and apoptotic death induced by H_2O_2, cells were treated with 0.5 mM H_2O_2 for 2 hrs in HBSS or were incubated for 18 h in normal culture medium following exposure of cells to 0.5 mM H_2O_2. Cells were stained with a fluorescent dye Hoechst 33258, which specifically binds to DNA. The nuclei of untreated control cells showed normal morphology (Fig. 1A). The nuclei of cells treated with 0.5 mM H_2O_2 for 2 hrs (Fig. 1B) could not be distinguished from those of control cells. In contrast, when cells were incubated in normal culture media for 18 hrs following exposure of cells to 0.5 mM H_2O_2 for 2 h, the nuclei of cells were disrupted and fragmented, exhibiting typical features of apoptosis (Fig. 1C). Cell viability estimated by trypan blue exclusion was approximately 61 and 62% under these two conditions, respectively. Similar results were obtained from flow cytometric analysis (Fig. 1D–E).

2. Effect of quercetin on necrotic cell death

Fig. 2 shows the time course of H_2O_2–induced necrotic cell death. Cells were exposed to 1.0 mM H_2O_2, and cell viability was determined at various time points (0–180 min).

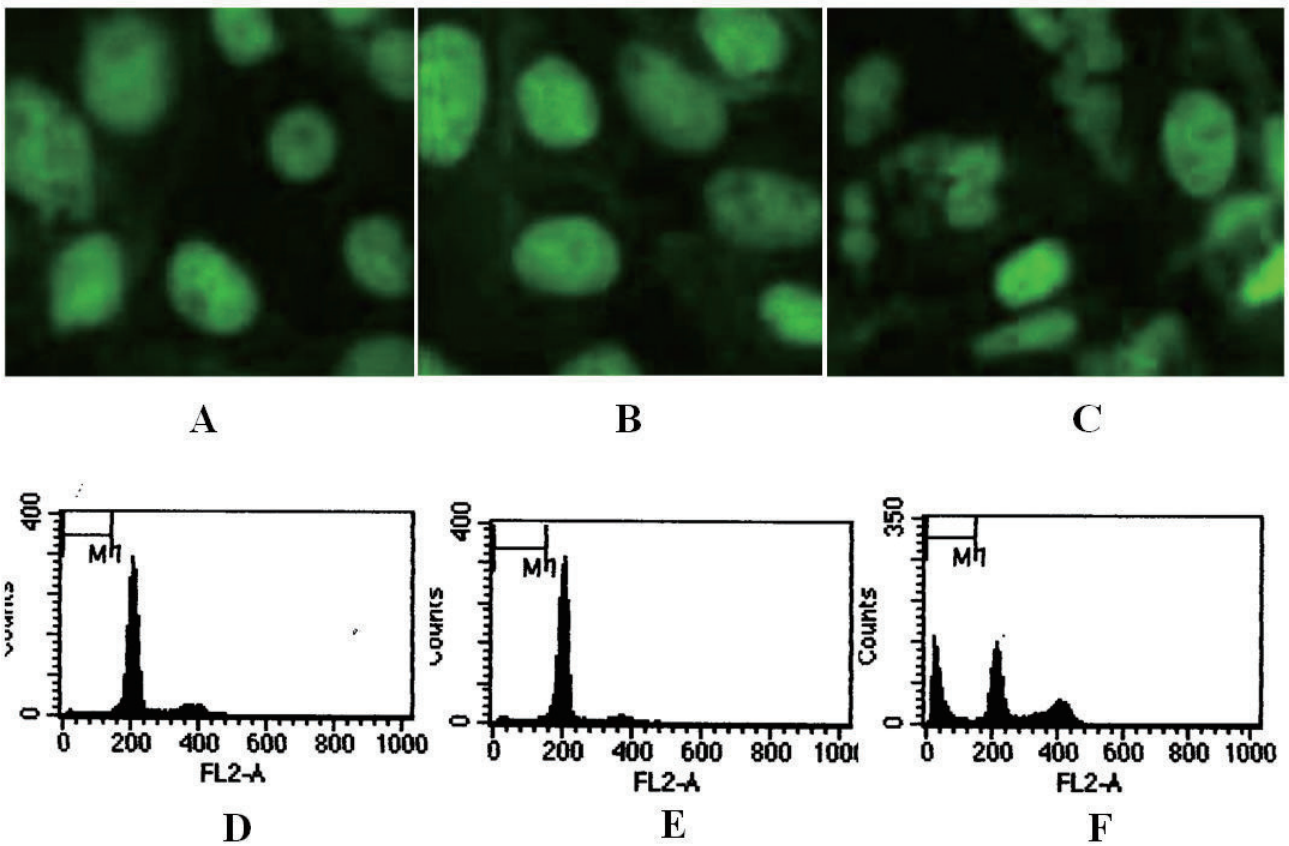

Fig. 1. Induction of apoptosis by H_2O_2. Hoechst 33258 staining (A–C) and flow cytometry (D–F) of cells exposed to H_2O_2. Apoptosis was measured in control (A, D), cells exposed to 1.0 mM H_2O_2 in HBSS for 2 hrs (B, E), and cells exposed to 0.5 mM H_2O_2 in HBSS for 2 hr and further incubated for 18 hr in normal culture medium (C,F).

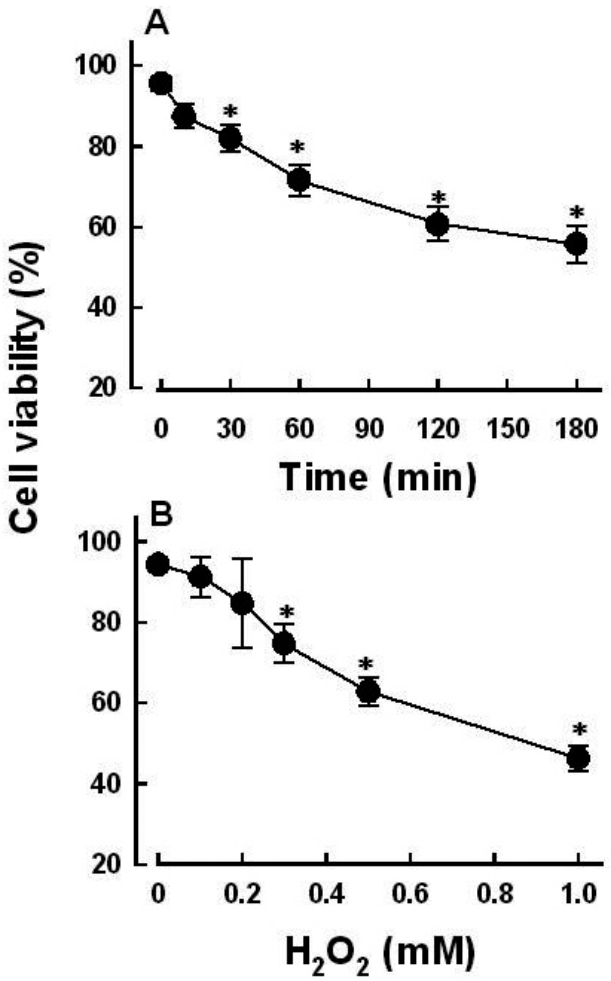

Fig. 2. Effect of H_2O_2 on necrotic cell death. Cells were exposed to 1.0 mM H_2O_2 for various time points (A) and various concentrations of H_2O_2 for 2 hrs (B). Cell viability was estimated by trypan blue exclusion assay. Data are mean±SEM of four experiments. *p<0.05 compared with control.

The significant loss of cell viability was present 30 min after exposure of cells to H_2O_2 and increased up to 180 min (Fig. 2). When cells were exposed to 0.1-1.0 mM H_2O_2 for 2 h, loss of cell viability increased in a dose-dependent manner and the significant loss was observed at 0.3 mM H_2O_2.

In order to examine the effect of quercetin on H_2O_2-induced necrotic cell death, cells were treated with 1.0 mM H_2O_2 in the presence of various concentrations of quercetin. As shown in Fig. 3, quercetin prevented H_2O_2-induced cell death in dose-dependent fashion and a significant protection was present at 5 μM (81.80±2.99 vs. 61.20±3.67% in H_2O_2 alone). When quercetin concentrations were increased up to 10 and 50 μM, the cell viability was significantly different from the control. However, quercetin did not exert any effect in the viability of normal cells untreated with H_2O_2.

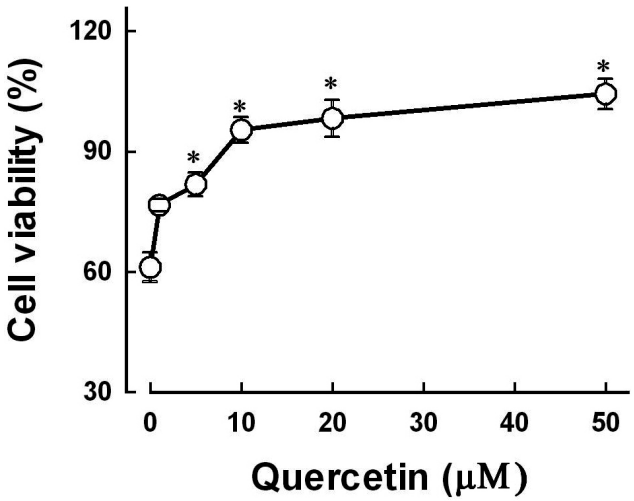

Fig. 3. Dose-dependent effect of quercetin on H_2O_2-induced necrotic cell death. Cells were exposed to 1.0 mM H_2O_2 for 2 hr in the presence or absence of various concentrations of quercetin. Cell viability was estimated by trypan blue exclusion assay. Data are mean±SEM of six experiments. *p<0.05 compared with the absence of quercetin.

In order to define the underlying mechanism of cytoprotective action of quercetin, effects of various agents including well-known antioxidants on necrotic cell death induced by H_2O_2 were examined. The results are summarized in Table 1. As expected, the H_2O_2 scavenger enzyme catalase prevented cell death. Similar protective effects were observed with the iron chelator DFO and the PARP inhibitor 3-AB, suggesting involvement of an iron-dependent mechanism and activation of PARP in H_2O_2-induced necrotic cell death. By contrast, antioxidants DPPD and Trolox did not affect the cell death, indicating that H_2O_2-induced cell death is not associated with lipid peroxidation. These results suggest that the cytoprotective effect of quercetin may be attributed to iron chelating ability rather

than antioxidant action.

The organic hydroperoxide tBHP has been known as an established inducer of lipid peroxidation (Halliwell *et al,* 1992). In order to examine the efficiency of DPPD on lipid peroxidation-induced cell death, cells were treated with tBHP in the presence of DPPD. Unlike H_2O_2-induced cell death, tBHP-induced death was significantly prevented by DPPD (Table 1), indicating that tBHP causes necrotic cell death through a lipid peroxidation mechanism. If protection by quercetin was resulted from H_2O_2 scavenging activity, tBHP-induced cell death could not be affected by quercetin. However, quercetin provided a significant protection against tBHP-induced cell death. DFO also was effective in preventing cell death (Table 1).

Table 1. Effects of various drugs on oxidant-induced cell death in T84 cells

Conditions	Necrosis (%)	Apoptosis (%)
Control	5.54±0.28	6.21±0.44
H_2O_2	46.49±4.56*	38.42±2.34*
+ Catalase (500 U/mL)	8.90±1.33†	7.54±0.66†
+ DPPD (10 μM)	49.35±0.76*	34.26±1.04*
+ Trolox (1 mM)	40.23±5.46*	39.95±0.98*
+ DFO (1 mM)	15.38±2.68*†	36.02±0.74*
+ 3-AB (1 mM)	10.10±1.42†	34.09±2.95*
+ Quercetin (10 μM)	11.45±1.29†	15.16±0.57*†
tBHP	39.29±2.33*	35.27±1.85*
+ DPPD (10 μM)	11.35±1.50*†	14.13±4.56*†
+ DFO (1 mM)	11.60±1.80*†	15.46±2.39*†
+ Quercetin (10 μM)	5.41±0.22†	15.44±1.84*†

Necrosis was induced by exposing cells to 1.0 mM H_2O_2 or t-butylhydroperoxide (tBHP) for 2 hrs in HBSS and apoptosis was induced by incubating cells for 18 hrs in normal culture medium following exposure of cells to 0.5 mM H_2O or 0.3 mM tBHP in HBSS in the presence or absence of various drugs. Necrosis and apoptosis were estimated by trypan blue exclusion assay and flow cytometry, respectively. Data are mean±SEM of six determinations. *$p<0.05$ compared with control; $^{\dagger}p<0.05$ compared with oxidant alone.

In the present study, the PARP inhibitor 3-AB prevented H_2O_2-induced necrotic cell death (Table 1), a result

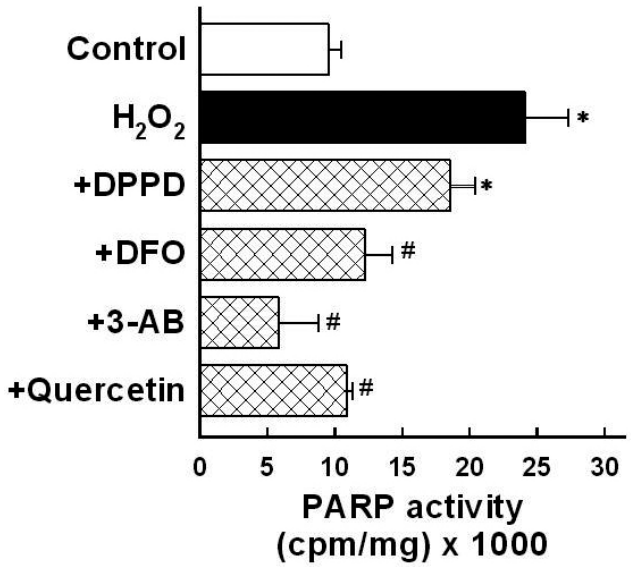

Fig. 4. Effects of various agents on H_2O_2-induced activation of poly (ADP-ribose) polyerase (PARP). Cells were exposed to 1.0 mM H_2O_2 for 2 hr in the presence or absence of *N,N'*-diphenyl-p-phenylenediamine (DPPD, 10 μM), deferoxamine (DFO, 1 mM), 3-aminobenzamide (3-AB, 5 mM), and quercetin (20 μM). Data are mean±SEM of four experiments. *$p<0.05$ compared with the absence of quercetin.

consistent with previous studies (Lee *et al,* 2001; Park *et al,* 2003). Therefore, we evaluated the effect of quercetin on PARP activation. Quercetin also inhibited the H_2O_2-induced activation of PARP similarly to DFO and 3-AB, but not DPPD (Fig. 4). These results suggest that H_2O_2 induces necrotic cell death by a mechanism dependent of PARP activation and independent of lipid peroxidation and that quercetin may exert the cytoprotective effect through inhibition of PARP directly or indirectly resulting from its iron chelating action.

3. Effect of quercetin on apoptotic cell death

Cells were exposed to various concentrations of H_2O_2 under experimental conditionsthat induce apoptosis and apoptotic cell death was estimated by flow cytometry. H_2O_2 induced apoptosis in a dose-dependent manner over concentrations of 0.1-0.5 mM (Fig. 5A). Quercetin

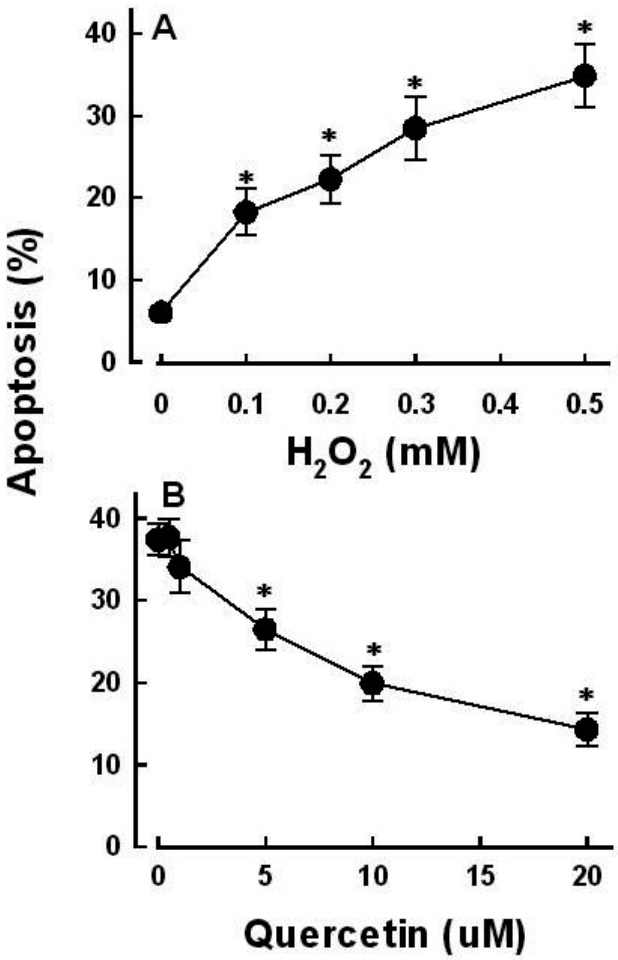

Fig. 5. Effect of quercetin on H_2O_2-induced apoptosis. (A) Dose-dependent effect of H_2O_2 on apoptosis. Cells were exposed to various concentrations of H_2O_2 in HBSS for 2 h and further incubated for 18 h in normal culture medium. Apoptosis was estimated by flow cytometry. Data are mean±SE of six experiments. (B) Dose-dependent effect of quercetin on H_2O_2-induced apoptosis. Apoptosis was induced as described in (A) with 0.5 mM H_2O_2 in the presence or absence of various concentrations of quercetin. Data are mean±SEM of six experiments. *p<0.05 compared with the respective control.

prevented H_2O_2-induced apoptotic cell death and its effect was dose-dependent (Fig. 5B), similarly to necrotic cell death.

In order to examine the role of lipid peroxidation and PARP in H_2O_2-induced apoptosis, effects of antioxidants and PARP inhibitor were evaluated. As shown Table 1, H_2O_2-induced apoptosis was not prevented by the antioxidants DPPD and Trolox. The apoptosis was also not affected by DFO and 3-AB, unlike necrosis. These results suggest that H_2O_2 induces apoptosis via mechanisms independent of lipid peroxidation and PARP activation. Quercetin also prevented tBHP-induced apoptosis that is dependent of DPPD and DFO. These data indicate that quercetin can prevent the lipid peroxidation-dependent and -independent apoptosis.

Discussion

Since a growing body of evidence suggests that ROS are implicated in the pathogenesis of stress- and chemically-induced gastrointestinal injury (van der Vliet and Bast, 1992) potent antioxidants may serve as a possible preventive intervention for gastrointestinal injury. Indeed, previous studies in mice and rats have reported that the dietary flavonoids such as quercetin protect colonic epithelial cells from carcinogenesis induced by azoxymethane. However, the precise molecular mechanism of quercetin cytoprotection remains to be defined.

Although flavonoids such as quercetin have been reported to have the abilityto inhibit lipid peroxidation and iron chelating properties (Formica and Reglson, 1955). they may also exhibit pro-oxidant activity. Previous studies showed that quercetin exacerbated membrane damage resulting from menadione-induced oxidative stress.Therefore, quercetin may have multiple action mechanisms.

In the present study, quercetin prevented H_2O_2-induced necrotic cell death in a dose-dependent manner (Fig. 3). Since flavonoids have free radical scavenging capacity (Fraga *et al,* 1987; Ratty and Das, 1988). and inhibits some biological processes triggered by H_2O_2 quercetin could prevent H_2O_2-induced cell death by directly scavenging H_2O_2 itself. However, quercetin also prevented cell death

induced by tBHP, similarly to its effect on H_2O_2-induced cell death (Table 1).

Since the cytoprotective effects of flavonoids have been reported to be associated with antioxidant capacity the effect of quercetin was compared with that of other well-known antioxidants. The necrotic cell death induced by H_2O_2 was not prevented by antioxidants DPPD and Trolox. Although lipid peroxidation of cell membrane has been considered to be an evidence for oxidant-induced cell injury dissociation of H_2O_2-induced cell injury from lipid peroxidation has been reported in various cell types (Zager and Burkhart, 1998; Min *et al,* 2000; Park *et al.* 2005). Lipid peroxidation can be a result or an epiphenomenon of cell death rather than a cause of cell injury . These results suggest that H_2O_2-induced cell death is not mediated by lipid peroxidation in T84 cells. Therefore, these data strongly suggest that the protective effect of quercetin against H_2O_2-induced cell death may be attributed to a mechanism other rather than its antioxidant action.

Iron appears to be the critical in the cytotoxic effect of H_2O_2 in T84 cells as the iron chelator DFO was markedly protective (Table 1). These data indicate that H_2O_2-induced necrotic cell killing is resulted from an iron-dependent mechanism and hence the protection of quercetin may be attributed to its iron chelating activity. Indeed, previous studies have demonstrated that the cytoprotection of flavonoids is related to iron chelating peroperties (Morel *et al,* 1993). Since PARP catalyzes the transfer of ADP-ribose from NAD to protein with the concomitant release of nicotinamide, the activation of this enzyme results in depletion of NAD and a consequent reduction in ATP, which may be involved in the pathogenesis of oxidant-induced injury. In fact, PARP activation has been demonstrated to be involved in cell death, predominantly necrosis, caused by H_2O_2 Interestingly, H_2O_2 induces cell injury through a PARP activation-dependent and lipid peroxidation-independent mechanism, whereas tBHP-induced cell injury is dependent of lipid peroxidation and independent of PARP activation in renal epithelial cells (Min *et al,* 2000; Park *et al,* 2003). In the present study, H_2O_2-induced necrotic cell death was prevented by the PARP inhibitor 3-AB (Table 1). Exposure of cells to H_2O_2 caused PARP activation, which was inhibited by DFO and 3-AB, but not DPPD (Fig. 4). These data suggest involvement of PARP activation in H_2O_2-induced death in T84 cells. We did not determine whether quercetin inhibits PARP activity directly or indirectly by iron chelation in this study. However, inhibition of PARP activation by quercetin is likely due to its iron chelating properties because many of the biological roles played by the flavonoids are associated with their iron-binding capabilities (Formica and Regelson, 1995).

Effects of quercetin on apoptosis are controversial. Quercetin facilitates apoptosis of tumor cells, in part through depression of an endogenous cytoprotective molecule, heat shock protein.The apoptosis-inducing action of quercetin has been also observed in colonic cells . On the other hand, quercetin prevents apoptosis induced by oxidants in renal epithelial cells and fibroblasts (Yokoo and Kitamura, 1997), liver epithelial cells and mesangial cells. The precise molecular mechanism of pro- and anti-apoptotic effect of quercetin remains poorly understood. Furthermore, it is unclear whether the ability of quercetin to inhibit apoptosis is attributed to antioxidant capacity.

The present study showed that quercetin prevents H_2O_2-induced apoptosis in a dose-dependent manner (Fig. 5B). Unlike necrotic cell death, H_2O_2-induced apoptosis was not affected by the iron chelator (DFO) and PARP inhibitor (3-AB). The data that the PARP inhibitor does not prevent H_2O_2-induced apoptosis are consistent with those reported in the intestinal epithelial cell line HT-29-18-C1. Antioxidants also were not effective in preventing H_2O_2-induced apoptosis, whereas tBHP-induced apoptosis was significantly prevented by antioxidant and iron chelator (Table 1). Taken together, these data suggest that

the protective effect of quercetin against H2O2−induced apoptosis is not associated with its antioxidant capacity including an iron chelating activity and a direct scavenging of H_2O_2. These results also indicate that quercetin prevents apoptosis via a mechanism different from that of necrosis

In conclusion, the present study demonstrated that quercetin prevented necrotic and apoptotic cell death induced by H_2O_2. The anti−necrotic effect of quercetin may be attributed to inhibition of PARP activation by its iron chelator activity. These results indicate that quercetin has the potential for inhibiting necrotic and apoptotic death of T84 cells and exerts the cytoprotective effect against both cell death modes through a different mechanism. The results of the present study provide information that quercetin may be useful in treatment and prevention of gastrointestinal injuries mediated by oxidants.

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