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Anti-Ulcerative Potential of Some Fruits and the Extracts

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1. Introduction

Concern about the effects of various foods on human health has risen significantly in recent years. Plant-based foods, including fruit and vegetables, are regarded as important for human health. It is believed that plant-based diets have positive effects on health due to their phytochemical components. Plant extracts that contain various phytochemicals have been used in a numbers of studies to assess their biological effect on health, but the precise roles of phytochemicals in human health are still unclear in many cases.

There are many reports indicating that various plant extracts and related phytochemicals can act as ulcer preventing agents. Studies have shown that extracts of plants used in ayurvedic medicine (traditional medicine native to India) display a certain level of efficiency on gastric ulcer prevention in animals (Ajaikumar et al., 2005; Bhatnagar et al., 2005; Mishra et al., 2009). Moreover, extracts from vegetables, such as artichoke (*Cynara Scolymus*) leaf (Ishida et al., 2010), rocket or arugula (*Eruca sativa*) (Alqasoumi et al., 2009), Indian cluster bean 'Guar' (*Cyamopsis tetragonoloba*) (Rafatullah et al., 1994), cabbage (*Brassica oleracea*) (Akhtar & Munir, 1989) and basil (*Ocimum basilicum*) (Akhtar & Munir, 1989), also have been reported to have certain effect on gastric ulcer prevention in rats.

Studies on fruit extracts using experimental gastric ulcer in rodents, have revealed antiulcerative activity, for banana (*Musa species*) (Pannangpetch et al., 2001), pomegranate (*Punica granatum*) (Ajaikumar et al., 2005), dates (*Phoenix dactylifera*) (Al-Qarawi et al., 2005), cluster fig (*Ficus glomerata*) (Rao et al., 2008), prickly pear (*Opuntia ficus indica*) (Galati et al., 2003), Indian cherry (*Cordia dichotoma*) (Kuppast t al., 2009), dried papaya (*Carica Papaya*) (Rajkapoor et al., 2003) etc.

There are various experimental models for gastric ulcers such as ethanol-, aspirin-, indomethacin- or stress-induced gastric ulcers. We have used ethanol-induced gastric ulcer (or gastric mucosal injury) in rats to find effective extracts from underutilized fruits, including immature fruits. Among these underutilized fruits, we have found that Chinese quince (*Pseudocydonia sinensis* (Thouin) C. K. Schneider) extracts were the most effective against gastric mucosal injury. Extracts from European (normal) quince (*Cydonia oblonga* Miller) fruit also showed activity, but in our experiments, Chinese quince extracts were superior to the quince (cv. Smyrna) extracts on a same weight basis.

Chinese quince and quince fruits have been used in traditional medicines in Asian and western countries, respectively. Chinese quince is believed to be native of China (Zhejiang province) and is now widely planted in Japan, China, and Korea. As for quince, the primary

area of natural growth seems to be the eastern Caucasus and Transcaucasus, and it is cultivated in all countries with worm-temperate to temperate climates (Khoshbakht and Hammer, 2006).



Fig. 1. Chinese quince (*Pseudocydonia sinensis* Schneid.) fruits on tree.

The Chinese quince fruit is inedible when raw because of its hard flesh, strong astringency, and high acidity. These characteristics are similar to those of the quince fruit, but Chinese quince has numerous stone cells that are larger than those in the quince fruit, making the flesh more unpleasant to eat. Therefore, these fruits, especially the Chinese quince fruit, are usually consumed as processed food products such as concentrated juice extracts, liquor, jam, jelly, glutinous starch syrup, crystallized fruit, and throat lozenges. The dried fruit has also been used in traditional medicine in the form of hot water extracts, for its antitussive and/or expectorant properties. Thus homemade medicines from Chinese quince fruit (including fruit liquor, decoction, syrup, and paste) have been said to have antitussive, expectorant, antispasmodic, and antidiuretic actions, and have been used for combating respiratory infections, intestinal dysregulation, and diuresis, and for treating people with a weak constitution. On the other hand, European quince fruits have been used as traditional medicines to treat cough (Kültür, 2007), constipation (Khoshbakht and Hammer, 2005) and also as stomach's comforter (Wilson, 1999).

In this chapter, studies on extracts of Chinese quince are presented and the efficacy of other fruit extracts and some of their chemical components on ulcer is also discussed.

2. Efficacy of fruit extracts and fruit products against HCl/ethanol induced mucosal injury in rats

2.1 Hot-water extracts from underutilized fruits and byproducts

2.1.1 Introduction

Attempts to find a use for underutilized fruits, including immature fruits picked through fruit thinning during fruit growth, have been made because those fruits have been known to

be rich in various phytochemicals. Moreover, there is an interest in residue of fruits (or pomace), by-products in the food industry, because it has become a big problem of waste disposal. For these reasons, a research project to discover a use for under-utilized fruits and industrial by-products of fruit processing has been carried out. In this research project, over 30 plant materials including underutilized fruits and horticultural by-products were collected and hot-water extracts were made to assess their biological activities. We investigated the antiulcerative potential of hot-water extracts from selected plant materials using an HCl/ethanol-induced ulcer model in rats for screening purpose. In addition, some chemical components and free radical scavenging activity were also measured.

2.1.2 Materials and methods

Plant materials were collected at various places in the Nagano prefecture, Japan. Hot-water extracts were obtained by boiling each plant material in four times its volumes of water for 1 hour. The suspended solution was filtered using two layers of cheesecloth and a filter paper, concentrated, then lyophilized. For determination of antiulcerative activity, male Wistar rats were orally administered 2.5 ml of water (control) or sample suspension containing 200 mg of extracts 30 min before gastric ulcer induction. The gastric mucosal lesions that lead to acute gastric ulcer were induced by oral administration of 1.5 ml of 150 mM HCl/ethanol (40:60, v/v) solution (Mizui & Doteuchi, 1983). Animals were sacrificed under anesthesia 60 min after the HCl/ethanol administration. Stomachs were removed, opened along the greater curvature, rinsed with physiological saline solution and stretched on balsa boards. The degree of gastric mucosal damage was evaluated from digital pictures using a computerized image analysis system. Percentage of the total lesion area (hemorrhagic sites) to the total surface area of the stomach except the forestomach was defined as the ulcer index. For chemical component analysis in the hot-water extracts, total polyphenol and polyuronide contents were determined using Folin-Ciocalteu method (Singleton & Rossi, 1965) and 3,5-dimethylphenol assay (Schott, 1979), respectively. Proanthocyanidin content was determined using butanol-HCl assay. Free radical scavenging activity (RSA) was determined using the 1,1-diphenyl-2-picrylhydrazyl (DPPH) method (Brand-Williams et al., 1995).

2.1.3 Results and discussion

In our experiment, many fruit extracts tested displayed some level of efficacy against gastric mucosal injury (antiulcerative activity) induced by HCl/ethanol in rats (Fig. 2). Among the fruit extracts, Chinese quince fruit extracts showed the strongest activity on the same weight basis although quince fruit, immature apple and apple pomace extracts also had a significant activity. Lack of clear activity in liquor residues of Chinese quince fruit suggests that the active ingredients were eliminated by dissolution in the alcoholic solution. Because boiling-water can extract polyphenolic compounds and cell wall polysaccharides effectively, the fruit extracts contained these components at various concentrations (4.4–106 mg/gDW for total polyphenols; 7.9–46 mg/gDW for total polyuronides). Study of the relationship between ulcer index and the presence of chemical components or radical scavenging activity indicated that total polyphenol and proanthocyanidin content tended to have a negative relation to the ulcer intensity induced by HCl/ethanol. Meanwhile, polyuronide content and radical scavenging activity do not seem to bear any relation with the ulcer index. However, it has been reported that antioxidant capacity is related to prevention of gastric ulcer because oxygen radicals generated from neutrophils have an important role in formation of

gastric lesions (Matsumoto et al., 1993). Our results indicate that not only radical scavenging activity, but also composition of antioxidants or other components were strongly related to the antiulcerative property of the fruit extracts. Hot-water extracts from Chinese quince fruit that were rich in procyanidins seemed to have a significant potential as an antiulcer agent. The effect of polyphenols and polysaccharides on experimental gastric ulcer is described later (in section 3). Additionally, it is not negligible that hot-water extracts from quince fruit or apple by-products also had moderate activity of ulcer prevention.

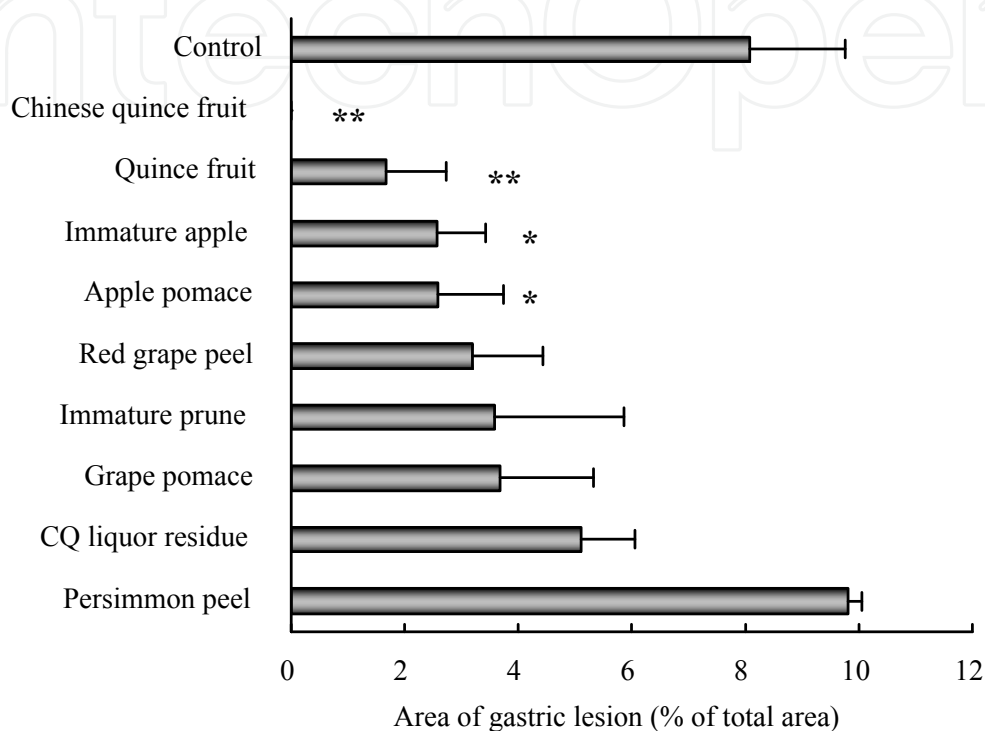


Fig. 2. Antiulcerative activity of hot (boiling)-water extracts from underutilized fruits or by-products. Rats were orally administered 2.5 ml of water (control) or a solution containing 200 mg of fruit extract 30 min before ulcer induction by 150 mM HCl/ethanol (40:60, v/v). Data are mean \pm SE (n=7 for control; n=5 for Chinese quince and quince fruits group; n=3 for other study group). * $P < 0.05$; ** $P < 0.01$ vs control (Student-t test). CQ, Chinese quince.

2.2 Boiling-water extracts and jelly of Chinese quince fruits

2.2.1 Introduction

Chinese quince and quince fruit are normally consumed after being processed into jam, jelly, fruit paste (quince cheese), or fruit liquor. During processing, the fruits are often heated or boiled for extended periods of time. Moreover, quince juice and jelly have been traditionally used as folk medicine for treating stomach illness (Kloss, 1999; Wilson, 1999). Quince marmalade has been believed to help digestion, to comfort or strengthen the stomach (Wilson, 1999). Although it is unclear whether the antiulcerative properties of the fruits was part of the folk medicine knowledge, study of food function including the antiulcerative properties of boiling-water extracts of these fruits is interesting and meaningful. Therefore, we investigated the chemical characteristics and preventive efficacy of boiling-water extracts and jelly made from the Chinese quince and quince fruits on HCl/ethanol induced gastric lesions in rats.

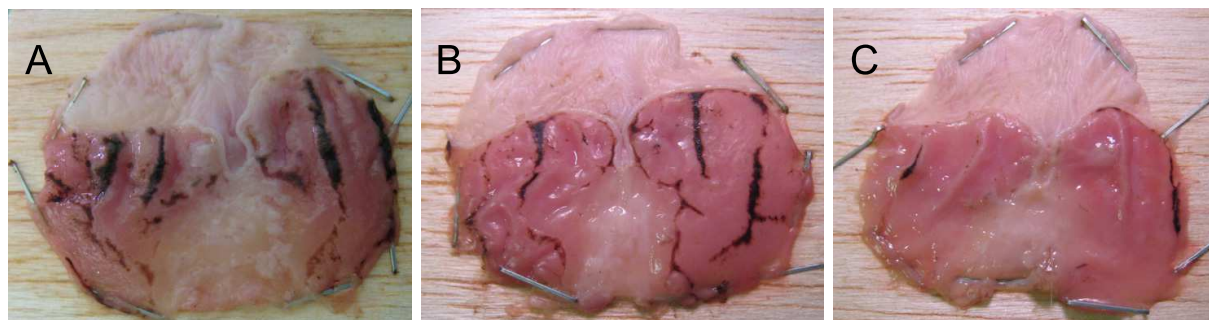
2.2.2 Materials and methods

Commercial ripe fruits of the Chinese quince 'Kegai' and quince 'Smyrna' were obtained at a local orchard in the Nagano prefecture, Japan. For boiling water extraction, fruit were cut into small pieces, put into 3 times their volumes of boiling water, and boiled for up to 4 hr. A small volume of boiling water was added every hour to make up for evaporation. The boiled fruit extract was filtered using 2 layers of cheesecloth and gently squeezed, brought to a volume of 800 ml (from 200 g fruit) and stored in a freezer until use. Fruit jelly was made using the boiled fruit extract as follows: 200 mL of extract (from 50 g of fruit) was mixed with 50 g of superfine sugar and reduced by boiling for 50 min to make 70 g of jelly. The procedure to determine antiulcerative activity and chemical components was as described above.

2.2.3 Results and discussion

In the experiment with Chinese quince extracts, administration of 2.5 ml of fruit extracts obtained by boiling for 2 hr significantly prevented the gastric mucosal lesions induced by HCl/ethanol but extracts obtained by boiling for 1 hr did not show significant activity (Fig. 3). Because boiling for extended periods of time has the advantage of breaking cell wall polysaccharides and to extract chemical components from the fruit tissue, the extracts obtained by boiling for 2 hr had more phytochemicals such as antioxidants than that obtained by boiling for 1 hr. In fact, amount of polyphenols extracted from 100 g of the fruit tissue after 1 hr and 2 hr of boiling was 791 mg (62.3%) and 985 mg (77.6%), respectively. Likewise, the amount of pectic polysaccharides extracted from 100 g of tissue after boiling for 1 hr and 2 hr was 291 mg (34.6%) and 365 mg (43.5%), respectively. Therefore, prolonged heating (boiling) in processing of Chinese quince fruit may be beneficial from a viewpoint of antiulcerative activity in HCl/ethanol induced ulcer.

Because the boiling water extracts of Chinese quince and quince fruits are rich in pectic polysaccharides and organic acids, they can easily form gels by addition of sugar and brief heating. To determine whether the gelling products (fruit jelly) retain the antiulcerative activity, Chinese quince and quince jellies made from the extract obtained by boiling for 2 hr were used for the study. The administration of jelly made from extracts of either fruits strongly prevented the development of gastric lesions (Table 1). This indicates that the preventive effect was retained even after jelly manufacturing. The antiulcerative activity of Chinese quince jelly was stronger than that of quince jelly. This may be due to the difference of polyphenolic content and radical scavenging activity in the jellies. The actual polyphenolic composition is currently being analyzed, but procyanidins (the major component in Chinese quince and quince fruit) in the jellies may be an important factor.



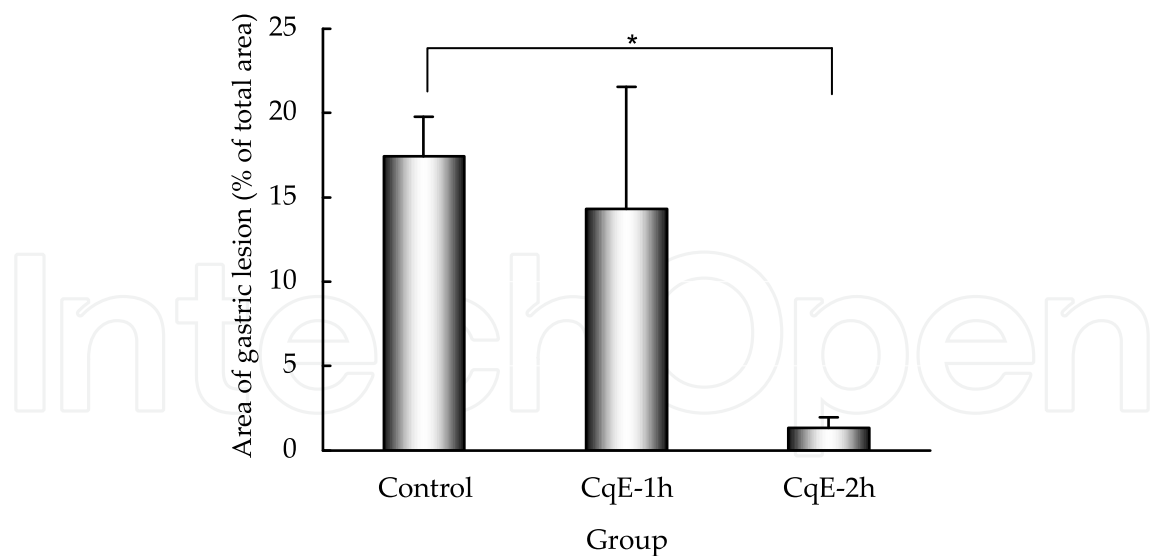


Fig. 3. Antiulcerative properties of boiling-water extracts of Chinese quince fruits on gastric lesions induced by HCl/ethanol in rats. Photographs shows mucosal surface of rat stomach. Rats were administered 2.5 ml of water (A; control) or fruit extracts obtained by boiling for 1 h (B) and 2 h (C) then gastric ulcer was induced by administration of 1.5 ml of HCl/ethanol. Histogram shows percentage of area of gastric lesion to total surface area of stomach. Data are mean \pm SE (n=19 for the controls; n=3 for each extract). * $P < 0.05$. CqE, Chinese quince extracts.

	Chinese quince	Quince
Reddish color (A458)	0.61 \pm 0.02	0.56 \pm 0.12
pH	2.9	3.2
Brix (%)	83 \pm 3.3	79 \pm 2.4
Viscosity (Pa s)	66.2 \pm 24	33.1 \pm 11
Polyphenol content ^a (mg/100 g)	704 \pm 18	166 \pm 2.5
Polyuronide content ^b (mg/100 g)	33.3 \pm 1.6	41.0 \pm 0.8
Radical scavenging activity (EC ₅₀) ^c	132 \pm 3.9	23.6 \pm 9.1
Antiulcerative activity ^d		
Area of gastric lesion ^e	0.04 \pm 0.01	0.47 \pm 0.22
Inhibition ratio (%)	99.5 \pm 0.16	93.5 \pm 3.1

^a (-)-epicatechin equivalent (Folin-Ciocalteu assay).

^b α -D-galacturonic acid equivalent (Dimethylphenolic assay).

^c Expressed as the dilution factor needed to decrease the initial DPPH concentration by 50%.

^d Rats (n = 5) were administered 2 ml of a diluted jelly solution (1 g jelly + 1 ml of water). Control rats (n = 19) were administered with water.

^e Percentage of lesion area in total surface area of stomach. The value for the control rats was 17.5 \pm 2.3 (%).

Table 1. Characteristics of Chinese quince and quince fruit jellies made from the extracts obtained by boiling for 2 hours.

2.3 Juice extracts of Chinese quince and apple fruits

2.3.1 Introduction

There are some commercial juice extracts of Chinese quince fruit available, but the production is very limited in Japan. Unlike other fruits such as apple, it is difficult to separate the juice of Chinese quince fruit from the pulp after homogenization using a blender. This is because their large amounts of fiber absorb the juice such that almost no liquid remains. Therefore, merely squeezing the mealy homogenate is not an effective means of juice extraction; hence, large quantities of sugar are often added to create a sucrose osmotic gradient, and then the juice is extracted. Practically, the crushed fruit obtained using a hammer crusher is added to a quantity of sugar approximately equal to 80% of the fruit weight and macerated for about three months. The mushy pulp is then squeezed in a pressing machine to obtain the juice extracts that contain approximately 60% sugar. This is the simplest method to obtain juice extracts from Chinese quince fruit. Because boiling-water extracts of Chinese quince fruit have a strong antiulcerative potential, we tried to see the effect of the juice extracts of Chinese quince fruit on prevention of the gastric mucosal lesions. In addition, the effect of apple juice was also investigated a comparison.

2.3.2 Materials and methods

Chinese quince fruit extract (juice extracted by using osmotic pressure as described above) and apple juice (cloudy type) were purchased from a local market affiliated to a juice factory in Nagano prefecture, Japan. The Chinese quince extract contained 60% (w/w) of sugar and had a pH of 3.4. The apple juice was made from 'Fuji' apples and contained >12% Brix and 0.25% organic acid. Treatment of rats including the induction of gastric mucosal injury was as described above except that the volume of sample solution administered was 3 ml. In addition to measurement of lesion area, myeloperoxidase (MPO) activity of mucosa was also measured because this enzyme indicates amount of infiltrating leukocytes. For this experiment, a crude enzyme solution was prepared from homogenized mucosa randomly collected with a razor blade from the inner surface of the frozen stomach. MPO activity was measured spectrophotometrically using 3,5,3',5'-tetramethylbenzidine (TMB) and 0.3% H₂O₂ in acetate buffer (pH 5). Free radical scavenging activity of the extract and juice was measured using DPPH radical. Polyphenolic composition was analyzed using PDA-HPLC.

2.3.3 Results and discussion

The HCl/ethanol-induced gastric lesions were strongly suppressed in rats that were given Chinese quince extracts and apple juice but the effect was stronger in those given Chinese quince extract (Fig. 4). The intensity of the gastric lesions, as quantified by the percentage of the injury surface area, was 20% in control rats versus 0.002% and 2.1% in rats given Chinese quince extract and apple juice, respectively. MPO activity in gastric mucosa (22.3 U/mg protein in controls) also was suppressed significantly ($P < 0.05$) in rats given Chinese quince extract (10.5 U/mg protein), and the activity tended to be suppressed in rats given apple juice (11.6 U/mg protein) as well.

The free radical scavenging activity of Chinese quince extract, expressed as the volume (ml) that can scavenge 50% of DPPH, was 4 times stronger than that of apple juice (Table 2). From these results, it appeared that the preventative effect of Chinese quince extract or apple juice might be due to the radical scavenging capacity and the suppression of leukocyte

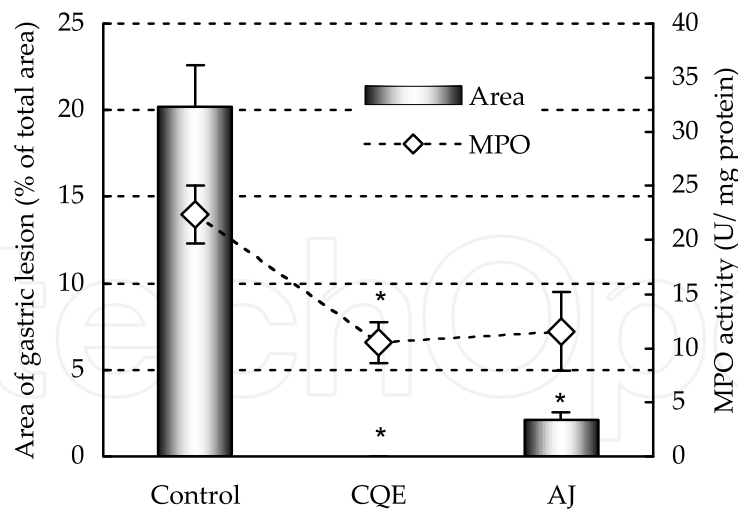


Fig. 4. Antiulcerative property of commercial Chinese quince extract and apple juice in rats.

Rats were administered 3 mL of water (control) or test solution (extract or juice) 30 min before gastric ulcer induction by HCl/ethanol. Vertical bars indicate SE (n=5). * $P < 0.05$ vs control. (from Hamauzu et al., 2008)

	Chinese quince extract	Apple juice
Free radical scavenging activity (EC_{50}) ^a	0.03 ± 0.001	0.12 ± 0.01
Soluble pectin (mg/100 mL) ^b	1.3 ± 0.07	4.9 ± 0.2
Total phenolics (mg/100 mL) ^c	342.2 ± 21.5	85.0 ± 6.4
Phenolic composition ^d		
(+)-Catechin	nd	0.57 ± 0.07
(-)-Epicatechin	3.7 ± 0.6	3.1 ± 0.09
Procyanidin B1 ^e	2.3 ± 0.2	1.3 ± 0.03
Procyanidin B2 ^e	7.3 ± 1.9	4.1 ± 0.07
Oligomeric procyanidins ^e	11.9 ± 3.2	tr
Polymeric procyanidins ^e	106.1 ± 38.8	nd
3-Caffeoylquinic acid ^f	4.9 ± 0.7	nd
5-Caffeoylquinic acid	5.5 ± 0.5	17.0 ± 0.2
Phloretin derivative ^g	nd	0.86 ± 0.01
Phlorizin	nd	0.70 ± 0.01

Data are mean ± SE. Abbreviations: nd, not detected; tr, trace.

^a Values are volume (mL) of sample that can scavenge 50% of DPPH.

^b Values are expressed as α -galacturonic acid equivalent.

^c Values are expressed as (-)-epicatechin equivalent in Folin-Ciocalteu method.

^d Values are results of HPLC analysis and expressed as mg/100 mL.

^e Values were calculated using standard curve for (-)-epicatechin.

^f Values were calculated using standard curve for 5-caffeoylquinic acid.

^g Values were calculated using standard curve for phlorizin.

Table 2. Free radical scavenging activity, soluble pectin content, total phenolic content and phenolic composition of Chinese quince extract and apple juice (from Hamauzu et al., 2008)

migration to the gastric mucosa, which could be indicated by lowered activity of MPO, a marker enzyme of leukocytes. It has been thought that leukocytes migrate to the site of inflamed mucosa after injury by HCl/ethanol and subsequently expand the lesion area by producing reactive oxygen species, including free radicals (Osakabe et al., 1998). Therefore, suppression of leukocyte migration may be an important mechanism of action in the antiulcerative activity as well as radical scavenging capacity of the fruit extract and juice. There was a remarkable difference not only in polyphenolic content but also in the chemical composition of Chinese quince extract and apple juice (Table 2). The major polyphenols in Chinese quince extract were polymeric procyanidins, whereas predominant component in apple juice was 5-caffeoylquinic acid (chlorogenic acid). This difference might be the cause of the different strength of the two fruit extracts in terms of antiulcerative activity. Although apple juice had relatively weaker activity than Chinese quince extracts, the preventive effect of apple juice against HCl/ethanol-induced gastric lesions is also worth noting.

3. Effect of fruit components on the experimental gastric ulcer in rats

3.1 Polyphenolic compounds

Some polyphenolic compounds have been reported to have antiulcerative activity and are believed to be the main factor of the beneficial effects of medicinal plants in some cases. Extracted polyphenols or particular polyphenols belonging to the flavonoids family of compounds (such as quercetin, rutin, naringenin) (de Lira Mota et al., 2009), catechin and proanthocyanidins (Saito et al., 1998; Iwasaki et al., 2004) and phenolic acids (such as caffeic, ferulic, *p*-coumaric acids) (Barros et al., 2008) were reported to have certain efficacy in animal models. For example, Alarcón de la Lastra et al. (1994) reported that oral pretreatment with the highest dose of quercetin (200 mg/kg), 120 min before absolute ethanol administration, was most effective in necrosis prevention. Moreover, flavonoids such as quercetin, flavone and flavanone have been shown to inhibit growth of *Helicobacter pylori* in a dose-dependent manner *in vitro* (Beil et al., 1995). (+)-Catechin has been reported to protect gastric mucosa against ischaemia-reperfusion-induced gastric ulcers by its antioxidant activity and mucus protection (Rao et al., 2008). Proanthocyanidins (condensed tannins) are polymers of a variable number of flavan-3-ol (catechins) units. The most abundant of proanthocyanidins are procyanidins which are widely distributed in the plant kingdom. Saito et al. (1998) studied the antiulcer capacity of pure procyanidin oligomers and showed that the antiulcer activity of a series of procyanidins increased as the degree of polymerization of the catechin unit increased. Oligomers longer than three catechin units showed a strong protective effect against stomach mucosal injury. In our research, we have shown that administration of highly polymerized procyanidins isolated from pear fruit (cv. Winter Nélis) with 60%(v/v) acetone after washing with 80%(v/v) methanol strongly suppressed the induction of gastric mucosal lesion (Hamaizu et al., 2007). The preventative effect of these molecules was clearly in histological sections (Fig. 5).

Moreover, semi-purified Chinese quince polyphenols that mainly consist of polymeric procyanidins also showed strong antiulcerative activity in a dose-dependent manner (Fig. 6). The effect was observed in the ulcer index (area of gastric lesion) and myeloperoxidase activity. Apple polyphenols also showed antiulcerative activity but it was not dose-dependent. This may be due to the presence of chlorogenic acid, the predominant component in apple polyphenols (see below).

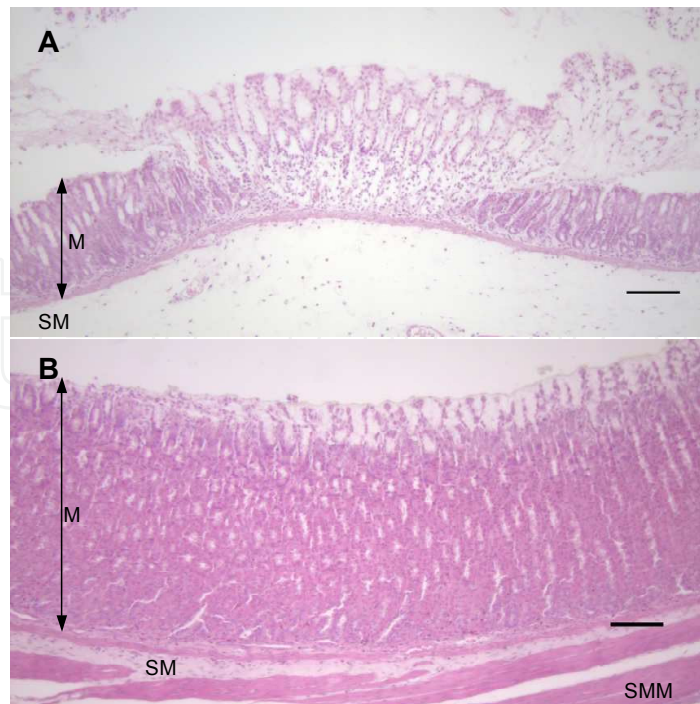


Fig. 5. Histological section analysis of rat gastric mucosa after treatment of HCl/ethanol. (A) Water was administered before induction of gastric mucosal lesions by HCl/ethanol. (B) Pear procyanidins, in an aqueous solution, were administered before induction of the lesion. M, mucosal layer; SM, submucosal layer; SMM, smooth muscle layer. Bar: 100 μ m.

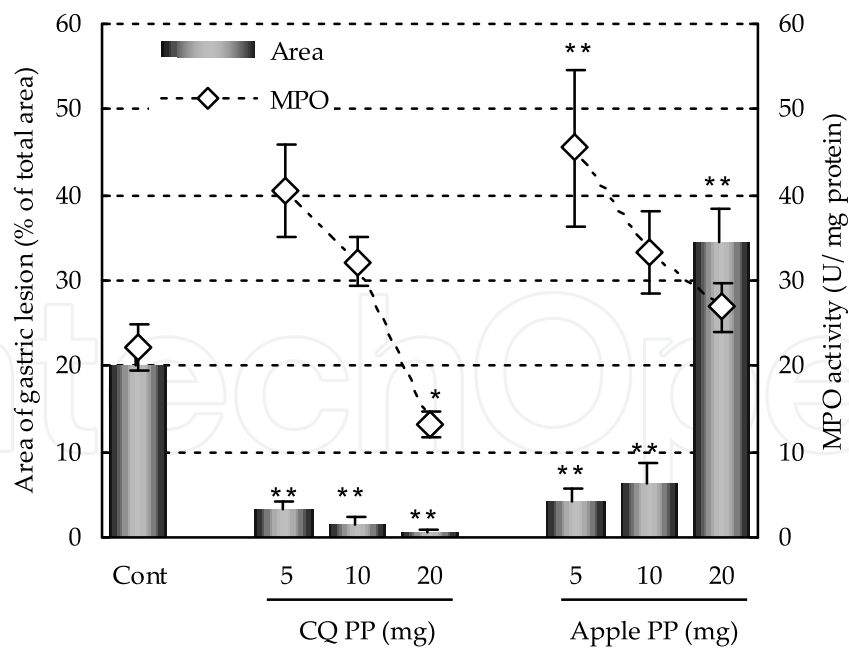


Fig. 6. Intensity of gastric lesions and mucosa myeloperoxidase activity (MPO) in rats that were administered 1.5 ml of water (control) or a solution of semi-purified Chinese quince polyphenols (CQ PP) or apple polyphenols (Apple PP) before treatment with HCl/ethanol. Bars indicate SE (n=15 for control group; n=5 for CQ PP and Apple PP group). * $P < 0.05$; ** $P < 0.01$ vs control.

The efficacy of procyanidins that have a high mDP may be due to both radical scavenging activity and affinity to the gastric mucosa. Procyanidins have affinity to protein (because they are a kind of tannin) and the affinity is known to depend in their degree of polymerization. Saito et al. (1998) reported that procyanidins such as pentamers and hexamers strongly bound to BSA. The highly polymerized procyanidins isolated from 'Winter Nélis' pear had a very high value of mean degree of polymerization (mDP = 89). Moreover, the mDP of procyanidins contained in semi-purified polyphenols from Chinese quince fruit was approximately 19, whereas that in apple polyphenols was 3–4. Their affinity to protein was actually affected by the mDP (Fig. 7 upper panel). Because of their high affinity to protein, fruit procyanidins having high mDP may have potential to bind to the mucosa. Additionally, radical scavenging activity of semi-purified Chinese quince polyphenols was stronger than that of apple polyphenols (Fig. 7 lower panel). Therefore, Chinese quince polyphenols may be superior to apple polyphenols in gastric protection because of the radical scavenging activity and its continuance on the gastric mucosa.

Thus, the mechanism of protection of the mucosa by fruit procyanidins may be both physical and chemical. By binding strongly to the mucosa, procyanidins build a protective layer against ethanol, reducing leukocyte migration, and then deploying a local antioxidant protection against free radicals. The real chemical pathway for activation and migration of leukocytes is not well understood, and it is difficult to say at which level procyanidins prevent this migration.

In our research, we have observed that chlorogenic acid-rich phenolic extract or chlorogenic acid standard showed a negative effect on prevention of gastric lesions when it was administered in excess dose.

Chlorogenic acid (5-caffeoylquinic acid) is a phenolic compound and is widely distributed in plant kingdom. It is observed in coffee beverage, blueberries, apples and ciders (Clifford, 1999). Coffee beans are one of the richest dietary sources of chlorogenic acid and for many consumers must be the major dietary source for this molecule. Chlorogenic acid has been reported to have a series of biological effects *in vitro* and *in vivo*, such as antioxidant capacity, radical scavenging activity, antimutagenic/anticarcinogenic effect, inflammation inhibiting and endothelial protective properties, etc. (Chang & Li, 2005), and thought that the compound might contribute to body health promotion to some extent. Zhao et al. (2008) has reported that chlorogenic acid has the down-regulative effects on the H₂O₂- or TNF- α -induced secretion of interleukin (IL)-8, a central pro-inflammatory chemokine involved in the pathogenesis of inflammatory bowel diseases, in human intestinal Caco-2 cells. In relation to the gastric ulcer prevention, Graziani et al. (2005) reported that chlorogenic acid was equally effective as apple extracts in preventing oxidative injury to gastric cells.

However, in some cases, chlorogenic acid seems to be ineffective in preventing gastric ulcers in animal models. Ishida et al. (2010) reported that oral administration of chlorogenic acid (4 mg/kg or 16 mg/kg, respectively) was ineffective to prevent absolute ethanol-induced or restraint plus water immersion stress-induced gastric ulcer in male Sprague-Dawley strain rats.

In our experiment, administration of a high dose (20 mg/rat; approx. 80 mg/kg b.w.) of chlorogenic acid tended to enhance the gastric lesion induced by HCl/EtOH in male Wistar rats. We also observed that a high dose (20 mg/rat) of semi-purified apple polyphenols (rich in chlorogenic acid) enhanced the ethanol-induced gastric lesions in rats. These findings suggest that chlorogenic acid has potential to increase some factors that progress gastric

lesions in ethanol-induced ulcer model when it administered at high dose. The actual mechanism is unclear, but chlorogenic acid seems to stimulate gastric acid secretion. It has been reported that chlorogenic acid affects the expression of gastric acid secretion-related proteins in human gastric cancer cell (Rubach et al., 2008). The excessive secretion of hydrochloric acid, the main constituent of gastric acid, in the stomach is considered an important factor in the formation of peptic ulcer (Welgan, 1974).

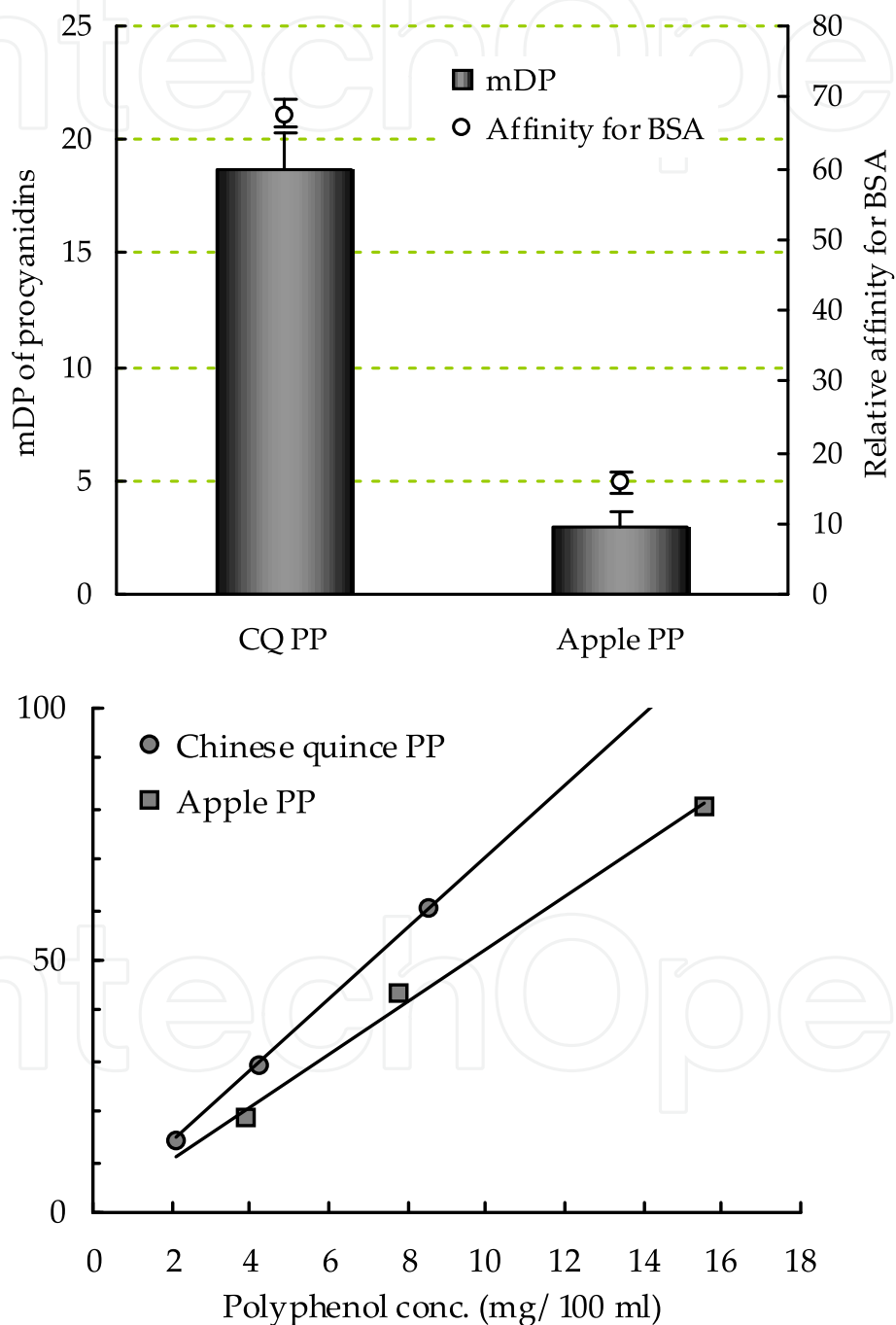


Fig. 7. Mean degree of polymerization (mDP) of procyanidins, relative affinity for bovine serum albumin and free radical scavenging activity of semi-purified Chinese quince polyphenols (CQ PP) and apple polyphenols (Apple PP).

Although high dose of chlorogenic acid or apple polyphenols have the potential to promote gastric mucosal lesions, normal consumption of apple polyphenol has been shown to prevent gastric ulcer in rats (Graziani et al., 2005). We also have confirmed that administration of cloudy apple juice suppressed gastric mucosal lesions induced by HCl/ethanol (section 2.3). Therefore, it should be emphasized that the natural concentration of phenolics in both apple fruit and juice may not cause any deteriorating effect on HCl/ethanol-induced gastric lesions and, in fact, may have some health benefit. This may indicate that excessively purified compounds may have adverse effects on health under particular conditions, even though they are known as health-promoting components.

3.2 Dietary fiber

Fruits contain high amount of soluble- and insoluble-fiber components. Soluble-fiber, such as pectic polysaccharides (pectin), might be an effective ingredient in gastric ulcer prevention because some soluble polysaccharides or mucilage were reported to have antiulcerative activity. For example, a galactomannoglucan with an estimated weight-average molar mass of 415,000 g/mol, obtained from an aqueous extract of the mesocarp of fruits of catolé palm (*Syagrus oleracea*), significantly inhibited gastric lesions induced by ethanol in mice, showing a gastroprotective property (da Silva & Parente, 2010). Lemnan, a pectic polysaccharide of duckweed *Lemna minor*, was also reported to be a potent gastroprotective agent for chemical and emotional stress models in animals (Khasina et al., 2003); it enhanced resistance of the stomach tissue to various ulcerogenic factors (emotional stress, indomethacin, pesticide 2,4-D).

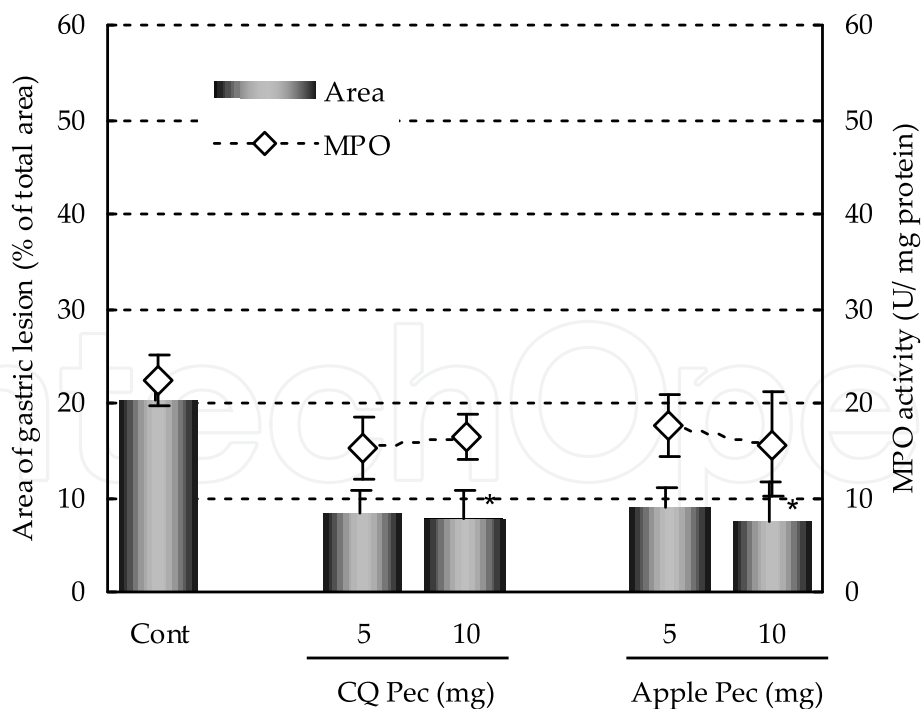


Fig. 8. Intensity of gastric lesions and myeloperoxidase (MPO) activity of mucosa of rats that were administered water (control), soluble pectin from Chinese quince fruit (CQ Pec) or commercial apple pectin (Apple Pec) before treatment with 150 mM HCl/ethanol (40:60, v/v). * $P < 0.05$ vs control.

In our research, soluble pectin extracted from Chinese quince fruit and commercial apple pectin both showed antiulcerative activity (Fig. 8). However, the effect seemed weaker than that of extracted polyphenols, especially in case of Chinese quince fruit. Therefore, pectic polysaccharides may partly contribute to antiulcerogenic activity together with polyphenols.

4. Conclusions

Many fruits, especially medicinal fruits, have been reported to have antiulcerative activity in animal experiment. Chinese quince fruit extract show strong activity for the prevention of gastric mucosal lesions induced by HCl/ethanol in rats. The effect is probably due to a high content of procyanidins that exhibit antioxidant activity and affinity to proteins. The preventative effect of fruit extracts on gastric mucosal lesions is retained even after prolonged heating (as observed in the effect of fruit jelly). Moreover, pectin, a cell wall polysaccharide, may enhance the effect of polyphenols on the prevention of gastric lesions. Meanwhile, some other fruit products such as apple juice and hot-water extract of quince also have a significant effect. However, a high dose of chlorogenic acid may promote the ethanol-induced gastric lesions. This indicates that excess intake of purified compounds should be avoided even if it is a natural antioxidant. Future research to elucidate the mechanisms of action of fruit polyphenols that prevent or increase the gastric lesions that lead to ulcer will be needed.

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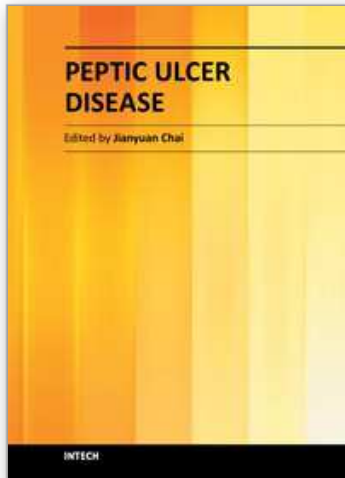
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