



Original Research Article

The use of Onion (*Allium cepa* L.) treatment can mitigate gastric mucosal injury in rats

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Onion (*Allium cepa* L.) is one of the most widely consumed culinary vegetables globally. Onions are a rich source of dietary flavonoids and other bioactive compounds. Its consumption offers protection against a wide range of gastrointestinal disorders. We used a rat model with gastric mucosal injury to simulate gastric ulcer disease in humans by triggering ulcers using various agents such as indomethacin, pylorus ligation, hypothermic restraintment and necrotizing agents (80% ethanol, 0.2 mol/L NaOH and 25% NaCl). Pre-treatment of rats with onion suspension (200 and 500 mg/kg) significantly mitigated enhanced ulcer index elicited by indomethacin, pylorus ligation, hypothermic restraintment and necrotizing agents. Furthermore, hypothermic restraintment-induced intraluminal bleeding was significantly attenuated by administration of onion suspension. Onion treatment significantly modulated changes in non-protein sulphhydryl and malondialdehyde levels of gastric tissue triggered by 80% ethanol. The biochemical findings were supported by an evaluation of stomach histopathology. The present data show that onion confers robust cytoprotection against gastric mucosal damage by a mechanism that is redox-sensitive. Dietary consumption of onions may, thus be beneficial against gastric ulcers in humans.

Key words: Gastric ulcer, folk medicine, onions, antioxidant, cytoprotection, antiulcer.

INTRODUCTION

The beneficial effects of herbs and spices on gastric ulcers have been supported by many studies. Ramifications of imbalances in gastric acid secretion and inadequate protection of the gastric mucosa together with oxidative stress include development of ulcerative lesions on the gastric mucosa. A wide variety of food products confer gastro-protection on account of their antioxidant properties. These effects have been exploited in folk medicine which relies on the curative properties of herbs (Al Mofleh, 2010; Wallace, 2013; Kangwan et al., 2014).

Onions (*Allium cepa* L.) are one of the most widely consumed vegetables. Onions are an important source of flavonoids. Only compounds belonging to flavonols, anthocyanins and dihydroflavonols have been reported to occur in onion bulbs (Slimestad et al., 2007). Alk(en)yl cysteine sulphoxides are important bioactive constituents of onions which impart flavour (Slimestad et al., 2007).

Compelling evidence suggests that the aforementioned chemical constituents of onions contribute to their different pharmacological effects. Compounds isolated from onions have been shown to possess anti-carcinogenic, hypolipidaemic, antithrombotic, antiasthmatic, antibacterial and antifungal properties (Dorsch et al., 1989; Ramos et al., 2006; Lanzotti et al., 2012; Thomson et al., 2013; Guercio et al., 2014). Previous studies have shown that dietary onion ameliorates lipid peroxidation and diabetic nephropathy (Babu et al., 1997). Furthermore, the constituent (+)-S-methyl-L-cysteine sulphoxide was shown to possess anti-hyperglycemic effects in alloxan-diabetic rats (Kumari et al., 1995). Onion extracts have been shown to attenuate cutaneous inflammation and edema formation by topical application, effects that are mediated by inhibition of prostanoid formation (Karagoz et al., 2009).

The favourable effects of onion consumption in

gastrological conditions are well documented. Recent epidemiological data provides robust evidence that consumption of onions reduces the risk of gastric cancer (Guercio et al., 2014). Although, dietary onion is associated with dyspepsia and triggering of gastroesophageal reflux, pharmacological studies of its chemical constituents showed anti-ulcer effects in rats alluding to its gastroprotective effects (Liu et al., 2013). However, the mechanisms of gastroprotective effects of onions in various models of experimentally-induced gastric ulcer remain elusive.

Beneficial effects of onion consumption and its pharmacological effects, therefore, lie at the interface of its wide consumption in various communities and its prescription in folk medicine. In this study, an animal model is used to simulate ulcerous lesions of the gastric mucosa to elucidate the pharmacological effects of acute onion (in suspension dosage form) treatment in rats and to unravel its protective role in gastric ulcers induced by various experimental triggers of gastric mucosal damage.

MATERIALS AND METHODS

Plant material and preparation of aqueous suspension

Fresh red onions (bulbs) were purchased from the local vegetable market at Riyadh and were identified by an expert taxonomist Dr. Mohammed Yousaf of the College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. The onions were sliced, shade dried, and pulverized to a very fine powder (Mesh # 70 micron). Then known amount of the powder was suspended in distilled water to obtain an aqueous suspension.

Animals

All experimental procedures were approved by the Ethics Committee of the Experimental Animal Care Society, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia. Wistar albino rats of either sex, approximately of same age, weighing 150-200 g were obtained from the Animal Care Center (ACC), College of Pharmacy, King Saud University. The Wistar albino rats were maintained under standard conditions of temperature, humidity and light (12 h dark, 12 h light) and fed with Purina chow and free access to water. Before testing, the animals were fasted for 36 h with access to water *ad libitum*.

Gastric wall mucus determination

The glandular segment of the stomach were removed and weighed, to determine gastric wall mucus in rats after receiving 80% ethanol only or ethanol plus onion suspension. Each segment was transferred immediately to 1% Alcian blue solution (in sucrose solution, buffered with sodium acetate at pH 5), and the excess dye was removed by rinsing with sucrose solution. The dye complexed with

gastric wall mucus was extracted with magnesium chloride solution. A 4-ml aliquot of blue extract was then shaken with an equal volume of diethyl ether. The resulting emulsion was centrifuged and the absorbance of the aqueous layer was recorded at 580 nm. The quantity of Alcian blue extracted per gram of glandular tissue (net) was then calculated.

Determination of anti-secretory activity

To determine anti-secretory activity, the 36-h fasted rats were anesthetized under light ether and the pylorus was ligated. Care was taken to avoid bleeding or occlusion of the blood vessels. Aqueous suspension of onion was administered intraperitoneally, immediately after pyloric ligation and the animals were then sacrificed 6 h after. The stomachs were removed, contents collected, measured, centrifuged and subjected to analysis for titratable acidity against 0.01 N NaOH at pH 7 and the total acid output was calculated.

Indomethacin-induced gastric mucosal ulceration

Indomethacin was suspended in 1.0% carboxymethyl cellulose in water (6 mg/ml) and administered orally to the fasted rats at 30 mg/kg body weight (0.5 ml/100 g). Control rats were treated similarly with an equivalent amount of the vehicle. The animals were sacrificed 6 h after the treatment. The stomachs were excised, rinsed with normal saline and ulcers were scored.

Gastric lesions induced by necrotizing agents

Each rat in the test group was given 1 ml of different necrotizing agents (80% ethanol, 0.2 M NaOH and 25% NaCl) that are known to produce gastric lesions. Onion suspension was given orally 30 min before administering the necrotizing agents. Animals were killed under ether anesthesia 1 h after treatment with the ulcerogenic agents. The stomach was excised and opened along the greater curvature. After washing with normal saline, the gastric lesions were quantified using a binocular magnifier and ulcers were scored. Lesions were also assessed by two observers blinded to experimental protocol.

Hypothermic restraint stress-induced ulcers

The method of Senay et al. (1967) was followed with slight modification. The animals were fasted for 36 h with access to water *ad libitum*. One hour after receiving oral onion suspension in treatment, 1 and 2 g/kg body weight, the rats were immobilized in restraint cages and placed inside a ventilated refrigerator maintained at 2–4°C. After 3 h, they were taken out and sacrificed. The stomachs were excised and examined for the severity of intraluminal bleeding according to the following arbitrary scale: 0 — no blood detectable; 1 — thin blood follows the rugae; 2 — thick blood follows the rugae; 3 — thick blood follows the rugae

Table 1. Effect of *A. cepa* suspension on the change in gastric wall mucus induced by 80% ethanol (mean \pm SE)

Treatment	Animals (n)	Dose (mg/kg, i.g)	Gastric wall mucus (mean \pm SE, μ g/g)
Control	6	—	376.55 \pm 16.56
80% ethanol only	6	—	262.14 \pm 23.76**
<i>A. cepa</i> suspension	6	250	306.16 \pm 14.07
	6	500	305.9 \pm 16.07

Six rats were used in each groups. ** $p < 0.05$ vs control (80% ethanol only) group,

with blood clots in certain areas; and 4 — thick blood (Chiu et al., 1983). After wiping the blood off, the total area of lesions in each stomach was scored as described above.

Estimation of non-protein sulfhydryl (NP-SH) groups

Gastric mucosal NP-SH was measured to analyze the oxidant antioxidant balance. The glandular stomach was removed and homogenized in ice-cold 0.02 M ethylenediamine-tetraacetic acid. The homogenate was mixed with distilled water and 50% (w/v) aqueous trichloroacetic acid and centrifuged; the supernatants were mixed with phosphate buffer (pH 8) and 5,5'-dithiobis (2-nitrobenzoic acid) (DTNB) added after which the sample was shaken. The absorbance was read within 5 min of addition of DTNB at 1/12 nm, against a reagent blank with no homogenate.

Determination of malondialdehyde

The method reported by Utey et al. (1967) was followed in the determination of malondialdehyde. The stomach tissues were removed and each tissue sample was homogenized in 0.15 M KCl (at 4°C; Potter-Elvehjem type C homogenizer) to give a 10% w/v homogenate. Aliquots of the homogenate (1 ml) were incubated at 37°C for 3 h in a metabolic shaker. Then 1 ml of 10% aqueous trichloroacetic acid (TCA) was added and mixed in. The mixture was then centrifuged at 800 g for 10 min. One milliliter of the suspension was removed and mixed with 1 ml of 0.67% thiobarbuturic acid in water and then placed in a boiling water bath for 10 min. The mixture was cooled and diluted with 1 ml distilled water. The absorbance of the solution was then read at 535 nm. The MDA content (nmol/g wet tissue) was then calculated by reference to a standard curve of the MDA solution.

Histopathological evaluation

The gastric tissues were fixed in 10% buffered formalin and processed using a VIP tissue processor. The processed tissues were then embedded in paraffin blocks and sections of about 5 μ m thickness were cut by employing an American-made optical rotary microtome. These sections were stained with hematoxylin and eosin using routine procedure (Culling, 1974). The slides were examined

microscopically for pathomorphological changes.

Statistical analysis

Values are given as arithmetic means \pm standard error of the mean (SEM). The data were statistically analysed by using a one-way analysis of variance (ANOVA) followed by Dunnett's and Student's t-tests.

RESULTS

Effect of *A. cepa* suspension on changes in gastric wall mucus

Firstly, the effect of onion suspension on ethanol-elicited gastric mucosal damage in rats was examined. Table 1 shows treatment with 80% ethanol triggered a significant decrease in gastric wall mucus, an effect that was significantly and dose-dependently blunted by the administration of *A. cepa* suspension (250 and 500 mg/kg).

Effects of *A. cepa* suspension on gastric secretion, acidity and gastric lesions

To determine whether onion treatment affects various parameters of gastric mucosal damage, volume of gastric content, titratable acidity and ulcer index in pylorus-ligated shay rats were assessed (Table 2). To this end, administration of onion (250 and 500 mg/kg) in rats significantly lowered the volume of gastric content in rats treated with onion suspension as compared to control pylorus-ligated shay rats administered with distilled water. To examine the effect of onion treatment on acid secretion, titratable acidity was analyzed. Administration of onion suspension significantly and dose-dependently reduced titratable acidity in pylorus-ligated shay rats as compared to control pylorus-ligated shay rats that were administered vehicle (distilled water) alone (Table 2). Examination of ulcer index revealed that administration of onion suspension significantly and dose-dependently ameliorated ulcer index with 500 mg/kg of onion suspension abrogating the ulcer index in pylorus-ligated shay rats (Table 2).

Table 2. Effect of *A. cepa* on gastric secretion, acidity and gastric lesion index in pylorus- ligated shay rats (mean \pm SE)

Treatment	Dose (mg/kg, i.g)	Volume of gastric content (ml)	Titrateable acidity (mEq/L)	Ulcer index
Control (Distilled water)	—	8.33 \pm 0.39	88.33 \pm 4.19	0.83 \pm 0.30
<i>A. cepa</i>	250	5.00 \pm 0.68**	61.66 \pm 2.54**	0.33 \pm 0.21
	500	3.00 \pm 0.44***	53.88 \pm 17.32	00***

Six rats were used in each groups. ** p<0.01***, p<0.001 vs control (distilled water) group.

Table 3. Effect of *A. cepa* suspension on indomethacin-induced gastric lesions (mean \pm SE).

Treatment	Animals (n)	Dose (mg/kg, i.g)	Ulcer index
Control (Indomethacin only)	6	—	36.50 \pm 1.58
<i>A. cepa</i> suspension	6	250	23.17 \pm 4.20
	6	500	9.83 \pm 2.26***

Six rats were used in each groups. ***p<0.001 vs control (indomethacin only) group.

Table 4. Effect of *A. cepa* on gastric lesions induced by necrotizing agents (mean \pm SE).

Treatment	Dose (mg/kg, i.g)	Ulcer index		
		80% EtOH	0.2 mol/L NaOH	25% NaCl
Control	-	7.00 \pm 0.44	7.16 \pm 0.54	5.66 \pm 0.84
	250	5.30 \pm 0.88	5.83 \pm 0.54	3.50 \pm 0.54
<i>A. cepa</i>	500	2.82 \pm 0.83***	4.16 \pm 0.47**	1.50 \pm 0.22***

Six rats were used in each groups. **p<0.01, *** p<0.001 vs control group.

Effect of *A. cepa* suspension on indomethacin-induced gastric lesions

In view of the protective effects of onion extract in pylorus-ligated shay rats, further examination of the effects of onion treatment in indomethacin-induced gastric ulcer in rats was carried out. To this end, acute treatment of rats with onion suspension significantly and dose-dependently attenuated indomethacin-induced damage of the gastric mucosa (Table 3). As depicted in Table 3, 500 mg/kg of onion extract reduced gastric ulcer index by 75% indicating the potent gastroprotective effects of onion administration in rats.

Effect of *A. cepa* suspension on gastric lesions induced by necrotizing agents

Furthermore, the study sought to elucidate the protective effect of onions by using other triggers of gastric injury in rats such as ethanol, sodium hydroxide and sodium chloride. As illustrated in Table 4, examination of ulcer index revealed that administration of onion suspension in rats significantly mitigated gastric mucosal damage triggered by all three necrotizing agents: 80% ethanol, 0.2 mol/L NaOH, and 25% NaCl. Administration of 500 mg/kg

of onion suspension reduced gastric ulcer index triggered by the aforementioned necrotizing agents by approximately 50% (Table 4).

Effect of *A. cepa* suspension on hypothermic restraint stress-induced intraluminal bleeding and gastric lesion in rats

To further define the pharmacological effects of gastroprotection mediated by onion suspension, ulcer index in gastric ulcer triggered by hypothermic restraint stress in rats was analyzed. As a result, administration of onion suspension (250 and 500 mg/kg) of rats prior to the induction of experimental gastric injury by stress-induced hypothermic restraint significantly and dose-dependently ameliorated gastric ulcer index in rats (Table 5). A consequence of macroscopic lesions of the gastric mucosa is bleeding. Therefore, the effects of onion treatment on intraluminal bleeding in rats subjected to stress elicited by hypothermic restraint were explored. As shown in Table 5, administration of onion suspension in rats significantly and dose-dependently curtailed intraluminal bleeding in rats as compared to control rats that received distilled water thus suggesting the robust gastroprotective effects of onion suspension in various

Table 5. Effect of *A. cepa* suspension on hypothermic restraint stress- induced intraluminal bleeding and gastric lesion in rats (Mean \pm SE).

Treatments (n = 6)	Dose (mg/kg, i.g)	Intraluminal bleeding score	Gastric lesion ulcer index
Control (Distilled water)	-	2.00 \pm 0.36	18.50 \pm 1.11
<i>A. cepa</i> suspension	250	1.16 \pm 0.30	14.00 \pm 1.86
	500	0.66 \pm 0.33*	10.16 \pm 0.60***

Six rats were used in each groups. *p<0.05, *** p<0.001 vs control (distilled water) group.

models of gastric ulcer in rats.

Effect on *A. cepa* on histological assessment

The results are tabulated in Table 6. The stomach of control animals showed normal rat gastric mucosa, changes induced following oral treatment with 80% ethanol and the protective effect of 250 and 500 mg/kg onion suspension.

Effect of *A. cepa* on the NP-SH concentration in gastric ulcer

To disclose the underlying mechanisms of protective effects of onion administration on the gastric mucosa of rats, additional series of experiments were performed to quantify NP-SH concentrations in gastric ulcer triggered by 80% ethanol. To this end, estimation of gastric NP-SH in gastric ulcers of rats treated with 80% ethanol was significantly lower than in untreated (control) rats (Table 7). Treatment with onion suspension significantly and dose-dependently blunted the decrease in 80% ethanol-triggered NP-SH depletion.

Effect of *A. cepa* on MDA concentration in gastric ulcer

To further characterize the mechanisms of gastroprotective effects of onions MDA concentration in gastric ulcer samples was analyzed. As shown in Table 8, treatment of rats with 80% ethanol significantly increased MDA concentration, an effect that was significantly and dose-dependently inhibited by treatment with 250 and 500 mg/kg onion suspension. These data suggest the participation of redox-sensitive mechanisms in the amelioration of gastric ulcers mediated by onion suspension in rats.

DISCUSSION

A fine balance between cytoprotective mucus lining and gastric acid secretion orchestrates protection from development of ulcerous gastric lesions. The present study unravels the protective effects of acute onion administration in rats and mechanisms by which onion treatment confers cytoprotective effects on the gastric mucosa against experimentally-induced ulcers. By utilizing

a previously established rat model simulating gastric ulcers in humans, we elucidate hitherto the unknown regulatory mechanism of antioxidant properties that foster cytoprotection mediated by onion suspension.

This study demonstrates that onion treatment enhances the abundance of cytoprotective mucus in the gastric lining. This effect of onion treatment may be directly relevant to its gastroprotective effects in acute gastric injury triggered by multiple inducers *in vivo*. It was observed that gastric injury triggered by indomethacin was counteracted by administration of onion suspension in rats. This effect may be mediated by the effects of onion on prostaglandin metabolism by modulation of the cyclooxygenase enzyme. This may further explain other biological effects of onions on chemoprevention of colon cancer which involves cyclooxygenase in its pathogenesis (Wargovich, 2001). Dietary flavonoids present in onions were previously shown to directly modulate cyclooxygenase-mediated prostaglandin formation and are thus putative targets for cancer prevention onion-based nutraceuticals (Al-Fayez et al., 2006). The flavonoid quercetin derived from onions was reported to downregulate cyclooxygenase 2 transcription in human lymphocytes *ex vivo* (de Pascual-Teresa et al., 2004), thus providing further evidence of suppression of prostaglandin metabolism in the biological effects of onion consumption. In addition to flavonoids, other bioactive constituents such as thiosulfates and cepaenes were shown to directly counteract cyclooxygenase activity *in vitro* (Wagner et al., 1990).

The antioxidant activity of onions is relatively modest as compared to other spices and foods (Shobana et al., 2000). Nevertheless, this may be a decisive factor in the pharmacological effects of onion treatment in gastroprotection. We observed a robust modulation of malondialdehyde concentration suggestive of the effects of onion treatment on oxidative balance in gastric tissue. Mounting evidence supports the view that the anti-gastric ulcer effects of onion may be attributed to its anti-oxidant effects. Intriguingly, alk(en)yl thiosulfates derived from onions were shown to elicit superoxide production in polymorphonuclear leukocytes despite its effect on inhibiting platelet aggregation (Chang et al., 2004). Rutin, a compound derived from onions, was recently shown to exert protective effects on gastric mucosal injury induced by gastric ischemia-reperfusion, an effect that was mediated by its antioxidant activity and the involvement of

Table 6. Effect of *A. cepa* on ethanol-induced histopathological lesions in gastric mucosa of rats

Group #	Treatment and dose (mg/kg, body weight)	Histopathological lesions induced							
		Congestion	Haemorrhage	Edema	Necrosis	Inflammatory changes	Dysplastic changes	Erosions	Ulceration
1	Control (distilled water) (1 ml/rat).	-	-	-	-	-	-	-	-
2	Ethanol, 80% (1 ml/rat).	++	++	+	+	+	+	++	++
3	<i>A. cepa</i> (250) + ethanol, 80% (1 ml/rat)	++	+	-	-	-	-	-	-
4	<i>Al. cepa</i> (500) + ethanol, 80% (1 ml/rat)	++	+	-	-	-	-	-	-

- = Normal; + = Moderate effect; ++ = Severe effect; +++ = Intensely severe effect.

Table 7. Effect of *A. cepa* on the NP-SH concentration in gastric ulcer induced by 80% ethanol (Mean ± SE)

Treatment	Animals (n)	Dose (mg/kg, i.g)	NP-SH concentration (µmol/100 mg wet tissue)
Control	6	-	8.59±0.33
80% Ethanol only	6	-	6.38±0.27***
<i>A. cepa</i>	6	250	6.80±0.47
		500	7.91±0.37*

Six rats were used in each groups. *p<0.05,*** p<0.001 vs control (80% Ethanol only) group

Table 8. Effect of *A. cepa* on MDA concentration in gastric ulcer induced by 80% ethanol (Mean ± SE)

Treatment	Animals (n)	Dose (mg/kg, i.g)	MDA (mean ± SE, µg/g)
Control	6	-	0.98±0.04
80% Ethanol only	6	-	6.05±0.28***
<i>A. cepa</i> + 80% Ethanol	6	250	5.63±0.34 ^b
		500	4.72±0.13**

Six rats were used in each groups. **p<0.05,*** p<0.001 vs control (80% Ethanol only) group

NOS/NO pathway (Liu et al., 2013). In this study, both the elevation of inducible NO synthase activity as well as the decrease of constitutive NO synthase in the gastric tissue were abated by rutin pretreatment (Liu et al., 2013).

The antioxidant property of onion treatment was shown to be beneficial in animal models of other

diseases (Ige et al., 2013). Onion treatment was shown to ameliorate cadmium-induced cardiotoxicity by attenuating apoptosis and by modulating redox-sensitive enzymes such as catalase, malondialdehyde, superoxide dismutase and glutathione peroxidase in the cardiac tissue (Alpsoy et al., 2014). Similarly, ischemia-reperfusion-

mediated cardiac injury was also prevented by onion treatment by affecting the production of reactive oxygen species as well as modulation of mitochondrial membrane depolarization, cytochrome c release and caspase-3 activation (Park et al., 2009). Interestingly, the gonadotoxic and spermotoxic effects of cadmium were shown to be

abated by onion treatment on account of its antioxidant effects (Ola-Mudathir et al., 2008). The oxidative damage triggered by cadmium in kidney tissues was reported to be significantly curtailed by onion treatment (Suru, 2008). Cadmium-induced hepatotoxicity was shown to be dose-dependently attenuated by treatment with onion extract (Obioha et al., 2009). Cellular ramifications of oxidative imbalance may be the inhibition of gap-junctional intercellular communication, an effect that was shown to be blunted by quercetin derived from onion peel (Kim et al., 2014). Along these lines, onion-derived quercetin may also prevent glutamate-induced hippocampal neuronal cell death (Yang et al., 2013). Besides, its antioxidant effects on tumor cell lines, onion extracts were shown to trigger DNA damage (Votto et al., 2010). The histopathological observations on the gastric mucosa further support the ability of onion suspension to protect gastric mucosal damage in rats.

In conclusion, the acute administration of onion suspension ameliorates gastric injury induced by multiple factors in rats and may be attributed to the antioxidant properties of onion suspension enriched with a wide range of bioactive constituents. Dietary consumption of onions may thus alleviate and/or confer protection against gastric ulcer in humans.

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