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Gastroprotective potential of frutalin, a d-galactose binding lectin, against ethanol-induced gastric lesions

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ABSTRACT

The present study was designed to verify whether frutalin (FTL) affords gastroprotection against the ethanol-induced gastric damage and to examine the underlying mechanism(s). Gastric damage was induced by intragastric administration of 0.2 ml of ethanol (96%). Mice in groups were pretreated with FTL (0.25, 0.5 and 1 mg/kg; i.p.), cimetidine (100 mg/kg; *p.o.*), or vehicle (0.9% of NaCl, 10 mL/kg; *p.o.*), 30 min before ethanol administration. They were sacrificed 30 min later, the stomachs excised, and the mucosal lesion area (mm^2) measured by planimetry. Gastroprotection was assessed in relation to inhibition of gastric lesion area. To study the gastroprotective mechanism(s), its relations to capsaicin-sensitive fibers, endogenous prostaglandins, nitric oxide, sulphydryls, ATP-sensitive potassium channels, adrenoceptors, opioid receptors and calcium channels were analyzed. Treatments effects on ethanol-associated oxidative stress markers GSH and MDA were measured in gastric tissue. FTL afforded a dose-unrelated gastroprotection against the ethanol damage. However, it failed to prevent the ethanol-induced changes in the levels of GSH and MDA. It was observed that the gastroprotection by FTL was greatly reduced in animals pretreated with capsazepine, indomethacin, L-NAME or glibenclamide. Considering the results, it is suggested that the FTL could probably be a good therapeutic agent for the development of new medicine for the treatment of gastric ulcer.

1. Introduction

Lectins are protein or glycoprotein substances, usually of plant origin, of nonimmunoglobulin nature. They are capable of specific recognition of and reversible binding to, carbohydrate moieties of complex glycoconjugates without altering the covalent structure of any of the recognized glycosyl ligands. Lectins also have the property of binding to sugars on cell membranes, thereby changing the physiology of the membrane, leading to agglutination, mitosis, or other biochemical changes in the cell [1].

Lectins are widely distributed in the Plant Kingdom and leguminous seeds are a particularly rich source of them. The main characteristics of this class of protein are based on their ability to interact with carbohydrates and thus combine with glycocomponents of cell surface, leading to their biological properties [2]. Lectins possess both inflammatory as well as antiinflammatory, immunomodulatory or immunostimulant properties.

Since the lectin-mediated interactions are involved in many pathological processes, carbohydrates and exogenous lectins, by blocking these glycobiological interactions, can be potentially useful as tools or therapeutic modulators in these processes [3].

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Many members of the genus *Artocarpus* have also been used as traditional folk medicine in South-East Asia for the treatment of inflammation, malarial fever and to treat the ulcers, abscess and diarrhea [4]. *Artocarpus incisa* L. is a wide spread plant, common in pan-tropical regions. *A. incisa* is popularly known as "fruta-pão" (breadfruit) and it is consumed cooked, by local population [2].

Frutalin is a homotetrameric α-D-galactose, a lectin belonging to the (JRL) family derived from *A. incisa*, with an apparent molecular mass of 66 kDa [5]. Frutalin may be successfully used in immunobiological research, on the recognition of cancer-associated oligosaccharides, similarly to other galactose-binding lectins [6]. Despite some reports on its cytotoxic [7], neuroprotective [8] and immunological effects [9] not much is known about its possible biological activities.

KM+, a lectin from *Artocarpus integrifolia*, may facilitate corneal epithelial wound healing in rabbits [10]. There are few previous reports regarding the gastroprotective effect of lectins. Because there is a similarity between KM + and frutalin, this study aimed to verify the possible gastroprotective effect of frutalin.

2. Experimental

2.1. Animals

Male Swiss albino mice (20–25 g) obtained from the Central Animal House of Fortaleza University were used. They were housed in environmentally controlled conditions (22 °C, 12 h light–dark cycle), with free access to standard pellet diet (Purina, São Paulo, Brazil) and water. Animals were kept in cages with raised floors to prevent coprophagy. Before the assays, they were fasted over a period of 15 h. The experimental protocols were in accordance with the ethical guidelines of Brazilian National Council for the Control of Animal Experimentation (Animal Ethics Committee of the State University of Ceará, protocol 08476547-0).

2.2. Frutalin purification

Highly purified lectin was obtained from *A. incisa* seeds as described earlier [2]. Briefly, ground dried seeds of *A. incisa* immersed in phosphate buffer solution (pH 7.4 PBS), 1:10 w/v were stirred for 6 h, at 4 °C and then centrifuged for 20 min (1500×*g*/4 °C). Supernatant was ultra filtrated through a YM10 membrane to half of its original volume and frutalin (MW 44 kDa) was purified from this crude extract on a Sepharose-D-galactose columm, eluted with 0.2 M D-galactose in PBS. After extensive dialysis against water, the eluted material was lyophilized and stored at −20 °C. Just before use frutalin was dissolved in sterile PBS, pH 6.8. Protein concentration was determined by Bradford's method and the purity of frutalin in solution was confirmed by the presence of only two bands (15.5 kDa and 12 kDa) after SDS-PAGE.

2.3. Gastric damage induced by ethanol

Groups of mice (n = 8) were pretreated with the vehicle (0.9% of NaCl, 10 mL/kg), cimetidine (100 mg/kg, *p.o.*) or frutalin (FTL 0.25, 0.5 and 1 mg/kg, i.p.) 30 min before the induction of gastric damage by oral administration of absolute ethanol (96%, 0.2 mL/animal) [11]. After 30 min, the animals were sacrificed, the stomachs excised, opened along the greater curvature and rinsed with saline (0.9%). Hemorrhagic or ulcerative lesions were measured using a computer planimetry program (ImageJ; National Institutes of Health — USA).

2.4. Gastric damage induced by indomethacin

Mice in groups (n = 8) were treated with FTL (0.25, 0.5 and 1 mg/kg, i.p.), cimetidine (100 mg/kg, *p.o.*) or vehicle (0.9% of NaCl, 10 mL/kg), 30 min after treatments, each animal received an oral dose of 30 mg/kg indomethacin and they were sacrificed 6 h later [12]. The stomachs were removed, immersed in 5% formalin for 30 min, and then opened along the greater curvature to register the incidence and extent of ulceration was recorded.

2.5. Effects of capsazepine pretreatment on frutalin (FTL) gastroprotection

Groups of mice (n = 8) were pretreated with vehicle (0.9% of NaCl, 10 mL/kg), FTL (0.5 mg/kg, i.p.) or capsaicin (5 mg/kg, *p.o.*) alone, or in their combinations with capsazepine (5 mg/kg, i.p.), prior to the oral administration of 0.2 ml of ethanol (96%). When given alone, FTL and capsazepine were administered 30 min before ethanol. Capsaicin was administered 1 h prior to ethanol.

2.6. Effects of indomethacin pretreatment on frutalin (FTL) gastroprotection

Groups of mice (n = 8) were pretreated with vehicle (0.9% of NaCl, 10 mL/kg), FTL (0.5 mg/kg, i.p.) or indomethacin (10 mg/kg, *p.o.*) alone or in combination prior to the oral administration of 0.2 ml of ethanol (96%).

2.7. Role of nitric oxide, K^+_{ATP} channels and sulfhydryl compounds on the gastroprotective effect of frutalin (FTL)

Groups of mice (n = 8) were pretreated with vehicle (0.9% of NaCl, 10 mL/kg), and FTL (0.5 mg/kg), alone, or in their combinations with L-NAME (10 mg/kg, i.p.), glibenclamide (5 mg/kg, i.p.) or N-ethylmaleimide (10 mg/kg, s.c.) prior to the oral administration of 0.2 ml of ethanol (96%). FTL, L-NAME, glibenclamide and N-ethylmaleimide were given 30 min prior to ethanol.

2.8. Role of α_2-receptors on the gastroprotective effect of frutalin (FTL)

Mice (n = 8/per group) were pretreated with vehicle (0.9% of NaCl, 10 mL/kg) or FTL (0.5 mg/kg, i.p.) alone, or in their combinations with yohimbine (2 mg/kg, i.p.) prior to induction of gastric damage with ethanol (0.2 ml of ethanol, 96%). FTL and yohimbine were given 30 min prior to ethanol.

2.9. Role of opioid receptors and calcium channels on the gastroprotective effect of frutalin (FTL)

Groups of mice (n = 8) were pretreated with vehicle (0.9% of NaCl, 10 mL/kg) or FTL (0.5 mg/kg, i.p.) alone, or in

their combinations with naloxone (2 mg/kg, i.p.) or verapamil (5 mg/kg, i.p.) prior to the oral administration of 0.2 ml of ethanol (96%). FTL, naloxone and verapamil were given 30 min prior to ethanol.

2.10. Role of lectin domain on the gastroprotective effect of frutalin (FTL)

To determine the involvement of sugar residues in the lectin effect, the binding between lectin and sugar was allowed. For this, animals were treated i.p. with FTL 0.5 mg/kg combined with 0.1 M of its ligand (D-galactose) previously incubated at 37 °C for 30 min. Mice (n = 8/per group) were pretreated with vehicle (0.9% saline, 10 ml/kg), FTL (0.5 mg/kg, i.p.) or FTL + D-galactose prior to induction of gastric damage with ethanol (0.2 ml of ethanol, 96%).

2.11. GSH assay

Reduced glutathione (GSH) content in stomach tissues as nonprotein sulfhydryls was estimated according to the method described by Sedlak and Lindsay [13]. A glandular segment from each stomach was homogenized in 5 ml of ice-cold 0.02 M EDTA solution (1 ml; 100 mg-1 tissue). Aliquots (400 μl) of tissue homogenate were mixed with 320 μl of distilled water and 80 μl of 50% (w/v) trichloroacetic acid in glass tubes and centrifuged at 3000 *g* for 15 min. Supernatants (400 μl) were mixed with 800 μl of Tris buffer (0.4 M; pH 8.9), and 20 μl of 5,5-dithio-bis(2-nitrobenzoic acid) (0.01 M) was added. After shaking the reaction mixture, absorbance was measured at 412 nm within 5 min of 5,5-dithiobis(2-nitrobenzoic acid) addition against a blank with no homogenate. Glutathione concentration was read off a standard curve and expressed as micrograms of GSH per gram of wet tissue.

2.12. MDA assay

The level of MDA in the homogenate from each group was measured using the method of Mihara and Uchiyama [14]. Determination of malondialdehyde precursor in tissues by thiobarbituric acid test was as follows. In brief, 250 μl of 10% homogenate of the tissue sample was added to 1.5 ml of 1% H_3PO_4 and 0.5 ml of 0.6% tert-butyl alcohol (aqueous solution), and then the mixture was stirred and heated on a boiling water bath for 45 min. After cooling, we added 2 ml of n-butanol, and the mixture was shaken and the butanol layer was separated by centrifugation. Optical density of the butanol layer was determined to be 535 and 520 nm, and the optical density difference between the two determinations was calculated (as the *tert*-butyl alcohol value). MDA concentrations were expressed as nanomoles per gram of tissue.

2.13. Statistical analysis

The results are presented as the mean ± S.E.M. of 8 animals per group. Statistical analysis was carried out using one way analysis of variance (ANOVA) followed by Student–Newman–Keuls *post hoc* test for multiple comparisons. *P*-values less than 0.05 ($p<0.05$) were considered as indicative of statistical significance.

3. Results and discussion

The intraperitoneal administration of FTL exhibited a protective effect against ethanol and indomethacin-induced gastric lesions (Table 1). Cimetidine (100 mg/kg), the positive control, also offered significant protection.

Pretreatment with capsazepine (Table 2) and L-NAME (Table 4) significantly blocked the gastroprotection produced by FTL. Indomethacin (10 mg/kg, p.o.) pretreatment completely abolished the protective effect of FTL (Table 3). Glibenclamide inhibited the gastroprotection produced by FTL (Table 4), but was unable to reverse completely the gastroprotective effect. In mice pretreated with the α_2-receptors antagonist yohimbine (Table 5) and with the N-ethylmaleimide (a sulfhydryl depletor, Table 4), the gastroprotective effect of FTL on ethanol damage was not blocked. The lectin effect was prevented by its binding sugar (Table 6).

Ethanol significantly depleted gastric NP-SHs and elevated the gastric mucosal MDA in mice that received the vehicle, when compared to normal control. The pretreatment with FTL (0.5 mg/kg) was not able to replenish the ethanol-induced depletion of NP-SH neither lowered the gastric mucosal MDA (data not shown).

The effects of frutalin, the α-D-galactose-binding lectin from *A. incisa*, on experimental gastric lesions were investigated for the first time. In this study, the gastroprotective efficacy of the lectin frutalin was evident against gastric injury caused by ethanol and indomethacin in mice. The lectin (FTL 0.5 mg/kg) demonstrated efficacy and manifested a dose-unrelated reduction in gastric injury caused by ethanol and indomethacin in mice. Our results are consistent with the earlier reports on the gastroprotective effects of other lectins observed in animal experimentation [15–17]. It was reported that the lectin from *Dioclea violacea* affords significant reduction in the gastric lesions produced by ethanol at a dose of 100 mg/kg [16]. Comparatively, the lectin analyzed in this study manifested a greater efficacy by affording gastroprotection at extremely smaller dose (0.5 mg/kg). Gastroprotective substances act by different, and many times, complementary mechanisms, promoting an increase in mucosal resistance or a decrease in aggressive factors [18].

Pre-synaptic α_2-receptors mediate several responses in the gastrointestinal tract and they are involved in the regulation of gastric acid secretion [19]. Pretreatment with α_2-receptors antagonist yohimbine failed to effectively block the gastroprotective effect of FTL (0.5 mg/kg) against ethanol damage.

Table 1
The effect of frutalin (FTL) on gastric damage induced by absolute ethanol or indomethhacin in mice.

Treatment	Dose (mg/kg)	Ethanol lesion area (%)	Indomethacin lesion area (%)
Control (vehicle)	–	32.88 ± 2.37	17.16 ± 1.75
FTL	0.25	33.67 ± 6.15	10.16 ± 1.88*
	0.5	10.52 ± 2.14**	8.00 ± 1.84*
	1	36.26 ± 4.21	12.33 ± 1.89
Cimetidine	100	18.20 ± 2.94*	8.66 ± 0.98*

The results are mean ± SEM for 8 animals/group. Statistical comparison was performed using ANOVA followed by the Student–Newman–Keuls multiple test. *$p<0.05$ and **$p<0.01$ compared with the control (vehicle) group.

Table 2
Role of capsaicin–sensitive sensory afferents on the gastroprotective effect of frutalin (FTL) against ethanol-induced gastric damage in mice.

Treatment	Dose (mg/kg)	Ethanol lesion area (%)
Control (vehicle)	–	16.80 ± 2.68
FTL	0.5	3.80 ± 1.43***
Capsazepine	0.5	20.16 ± 3.12
Capsazepine + FTL	5 + 0.5	11.90 ± 2.56

Data are presented as mean ± S.E.M. from 8 animals. ***$p<0.001$ compared with vehicle (control) group.

Table 3
Role of prostaglandins on the gastroprotective effect of frutalin (FTL) against ethanol-induced gastric damage in mice.

Treatment	Dose (mg/kg)	Ethanol lesion area (%)
Control (vehicle)	–	23.30 ± 6.50
FTL	0.5	2.7 0 ± 1.15***
Indomethacin	10	15.28 ± 4,38
Indomethacin + FTL	10 + 0.5	19.10 ± 5.48

Data are presented as mean ± S.E.M. from 8 animals. ***$p<0.001$ compared with vehicle (control) group.

Ethanol-induced gastric damage is also associated with a significant decrease in the mucosal sulfhydryl compounds (SH) and pretreatment with SH-blockers prevents the gastroprotection of SH-containing compounds [20]. In agreement with previous findings, the concentration of NP–SH in the gastric mucosa significantly decreased after administration of ethanol, and FTL did not inhibit the decrease in the NP–SH levels. In addition, pretreatment with an SH-blocker, N-ethylmaleimide, did not alter the mucosal protection afforded by FTL (Table 7).

Since yohimbine and N-ethylmaleimide were inactive in obliterating the FTL protection, we infer that mechanisms other than α_2-receptors and the increase in endogenous SHs participate in its gastroprotective activity. Treatment with FTL didn't decrease MDA formation, confirming that the lectin possess no antioxidant potential.

The FTL effect was reduced in mice pretreated with glibenclamide. It is suggested that the regulation of opening and closing K^+_{ATP} channels in the stomach can be a defense mechanism against external aggression to the gastric mucosa. It implies that FTL gastroprotection may be related to K^+_{ATP} channel activation. However, the blockade produced by glibenclamide, although significant, was only partial indicating a limited participation of K^+_{ATP} channels in the gastroprotective effect of FTL.

Table 4
Role of nitric oxide, K^+_{ATP} channels and sulfhydryl compounds on the gastroprotective effect of frutalin (FTL) against ethanol-induced gastric damage in mice.

Treatment	Dose (mg/kg)	Ethanol lesion area (%)
Control (vehicle)	–	30.59 ± 3.93
FTL	0.5	1.74 ± 0.77***
L-NAME	10	31.44 ± 8.98
Glibenclamide	5	23.11 ± 3.67
N-ethylmaleimide	10	47.64 ± 6.64*
L-NAME + FTL	10 + 0.5	22.37 ± 6.22
Glibenclamide + FTL	5 + 0.5	15.58 ± 3.17*
N-ethylmaleimie + FTL	10 + 0.5	3.90 ± 0.49***

Data are presented as mean ± S.E.M. from 8 animals. *$p<0.05$ and ***$p<0.001$ compared with vehicle (control) group.

Table 5
Role of α_2-receptors on the gastroprotective effect of frutalin (FTL) against ethanol-induced gastric damage in mice.

Treatment	Dose (mg/kg)	Ethanol lesion area (%)
Control (vehicle)	–	45.31 ± 8.61
Yohimbine	2	33.48 ± 1.78
FTL	0.5	15.16 ± 5.26**
Yohimbine + FTL	2 + 0.5	11.84 ± 6.01**

Data are presented as mean ± S.E.M. from 8 animals. **$p<0.01$ compared with vehicle (control) group.

L-NAME (10 mg/kg) significantly blocked the gastroprotection produced by FTL, suggesting NO participation in its gastroprotection. It is well known that NO is involved in the modulation of gastric mucosal integrity, and in the regulation of acid and alkaline secretion, mucus secretion and gastric mucosal blood flow [21]. In order to verify the role of prostaglandins in the gastroprotection afforded by FTL, mice were pretreated with indomethacin, a non-selective cyclooxygenase inhibitor. The results reveal that the gastroprotection by FTL against ethanol-induced mucosal injury was mitigated by indomethacin, suggesting a role for endogenous prostaglandins in gastroprotection.

Since the protection afforded by FTL is additionally indomethacin-sensitive, we assume that endogenous prostaglandins and nitric oxide act as activators of K^+_{ATP} channels and thus might contribute to enhanced gastric microcirculation.

Capsaicin acts on the sensory neurons stimulating the receptors of membrane TRPV-1, and in small doses, it has a gastroprotective effect by stimulating gastric microcirculation. In the stomach, the afferent sensory nerves sensitive to capsaicin are involved in the local defense mechanism against the formation of gastric ulcers, and the oral administration of capsaicin exercises a protective effect on the gastric mucosa against injury caused by ethanol [18]. Based on these data, we investigated the role of the capsaicin-sensitive afferent nerves in the gastroprotective effect of FTL in the model of gastric injury prompted by ethanol. For this, mice were pretreated with capsazepine, an antagonist of $TRPV_1$. The results reveal that the gastroprotection by FTL against ethanol-induced mucosa injury was suppressed when the $TRPV_1$ was blocked, suggesting a role for the capsaicin-sensitive afferent nerves in gastroprotection afforded by FTL.

Table 6
Role of opioid receptors and calcium channels on the gastroprotective effect of frutalin (FTL) against ethanol-induced gastric damage in mice.

Treatment	Dose (mg/kg)	Ethanol lesion area (%)
Control (vehicle)	–	32.42 ± 5.80
FTL	0.5	7.50 ± 2.12***
Naloxone	2	19.08 ± 4.61
Verapamil	5	18.35 ± 3.17
Naloxone + FTL	2 + 0.5	23.01 ± 5.71
Verapamil + FTL	5 + 0.5	17.53 ± 4.09

Data are presented as mean ± S.E.M. from 8 animals. *$p<0.05$ and ***$p<0.001$ compared with vehicle (control) group.

Table 7
Role of lectin domain on the gastroprotective effect of frutalin (FTL) against ethanol-induced gastric damage in mice.

Treatment	Dose (mg/kg)	Ethanol lesion area (%)
Control (vehicle)	–	14.47 ± 2.53
FTL	0.5	4.12 ± 1.06***
D-galactose 0.1 M + FTL	0.5	16.02 ± 4.02

Data are presented as mean ± S.E.M. from 8 animals. ***$p<0.001$ compared with vehicle (control) group.

The main characteristics of lectins are based on their ability to interact with carbohydrates and thus combine with glycocomponents of cell surface, leading to their biological properties [2]. The involvement of the lectin domain in the gastroprotective effect of FTL was demonstrated, since this effect could be reversed by the administration of lectin in combination with its specific ligand D-galactose.

In conclusion, the results of this study indicate a gastroprotective role for frutalin against gastric mucosal damage induced by ethanol and indomethacin. The observed gastroprotection is possibly mediated to a major extent by include the activation of capsaicin-sensitive gastric afferents, stimulation of endogenous prostaglandins, nitric oxide and opening of K^+_{ATP} channels.

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