Anti-inflammatory and non ulcerogenic activities of acetylbergenin

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Key words: Endopleura uchi, bergenin, acetylbergenin, anti-inflammatory, antiulcerogenic activity.

INTRODUCTION

Endopleura uchi (Huber) Cuatrec. (Humiriaceae), the Brazilian Amazon plant, is used in folk medicine to treat arthritis and gastric ulcer. Bergenin, one of the chemical constituents of E. uchi, has anti-inflammatory properties. Its acetylation results in acetylbergenin, which is extracted to investigate its potential anti-inflammatory and antiulcer properties using an assay for croton oil-induced ear edema, rat paw edema induced by carrageenan and dextran, carragenin-induced peritonitis, and stress-induced gastric ulcer. In ear erythema induced by croton oil, acetylbergenin presented a significant 75.60% inhibition (p<0.001). The oral administration of 6.8 mg/kg of acetylbergenin significantly inhibited the carrageenan-induced edema formation by 35.09% (p<0.05) and the dextran-induced edema by 33% (p<0.05). The migration of neutrophils toward the peritoneal cavity was inhibited in acetylbergenin (6.8 mg/kg) treated animals by 70% (p<0.01). In the stress-induced gastric ulcer, acetylbergenin inhibited 78.55% of gastric lesions. The results suggest that, the anti-inflammatory action of acetylbergenin appears to be dependent on cyclooxygenase (COX-2) inhibition. Furthermore, although the anti-inflammatory activity of acetylbergenin is a characteristic of nonsteroidal compounds, it causes little deleterious interference in the gastric mucosa.

Key words: Endopleura uchi, bergenin, acetylbergenin, anti-inflammatory, antiulcerogenic activity.
(Cuatrecasas, 1961). *E. uchi* is widely used by the people to combat myoma and arthritis, although only few biological studies are available on the properties of its extract. Bergenin (1) is a C-glucoside of 4-O-methyl gallic acid that has been isolated as the major component from the cortex of *E. uchi* and is used for treating gastrointestinal diseases such as gastritis, gastric ulcer, diarrhea, and constipation (Okada et al., 1973; Abe et al., 1980). In addition, studies report that bergenin reveals anti-inflammatory (Swarnalakshmi et al., 1984; Nunomura et al., 2009), antiarthritic (Nazir et al., 2007) and hypolipidemic effects (Jahromi et al., 1992). In our laboratory, bergenin (1) was isolated as the principal component from the aqueous extract of the *E. uchi* cortex and acetylbergenin (2) was obtained by acetylation of bergenin in order to increase its lipophilic and physiological activities. In the present study, the anti-inflammatory and ulcerogenic activities of acetylbergenin in various experimental models *in vivo* were investigated.

**MATERIALS AND METHODS**

**Extraction and isolation of bergenin (1)**

The extraction and isolation of bergenin (1) were carried out according to Borges et al. (2011). Air-dried powdered bark (1.6 kg) of *E. uchi* was extracted at room temperature with 10 L of distilled H2O for 6 days. After filtration, the extract was lyophilized to obtain 89 g of the aqueous lyophilized extract. The lyophilized extract (5 g) was fractionated on silica gel (70-230 mesh, 125 g) column resulting in 66 fractions, after elution with n-hexane (100%), n-hexane/EtOAc (20, 25, 27.5, 30, 35, 40, 45, 50, 55, 60, 65, 70, 80 and 90%) mixtures, EtOAc (100%), EtOAc/MeOH (5, 10, 20, 40, 50, 70, and 80%) mixtures and MeOH (100%). Fraction eluted with EtOAc (100%), EtOAc/MeOH (10%) and EtOAc/MeOH (20%) were combined affording bergenin (1) (1.02 g). Bergenin was purified by recrystallization from methanol and identified by comparison of its physical and spectroscopic data (IR, 1H and 13C NMR) with those reported in the literature (Ramaiah et al., 1979).

**Acetylation of bergenin**

The method described by Borges et al. (2011) was employed in this assay. In a round-bottomed flask of 125 mL, 700 mg of bergenin (1), 17.5 mL of acetic anhydride (Ac2O, 100% degree of purity, Synth, Brazil) and 6.5 mL of anhydrous pyridine (100% degree of purity, Synth, Brazil) were added. After agitation, the mixture was maintained for 24 h at room temperature and then transferred to a separator funnel of 125 and 25 mL of distilled water was added and the mixture was extracted with ethyl acetate (3 x 40 mL). The organic phases were collected, washed with distilled water (2 x 40 mL), 5% hydrochloric acid solution (1 x 40 mL) and then with distilled water (2 x 40 mL) until neutral pH was obtained. The organic phase was dried with anhydrous Na2SO4 and after filtration, the solvent was evaporated at room temperature in a chapel. The solid material obtained in the form of white crystals was recrystallized in methanol resulting in 1.13 g (yield 99%) of crystals of acetylbergenin (2) with 99% degree of purity.

**Animals**

Swiss albino mice (*Mus musculus*) male adults, weighing between 20 and 25 g and male Mac Coy rats (180 to 200 g), from the Evandro Chagas Animal Hospital of Belém, PA, Brazil, were used in this study. Male albino Wistar rats weighing between 180 and 200 g from the Multidisciplinary Center for Biological Research in the Laboratory Animal Science Area (Multidisciplinary Center for Biological Investigation in the Area of Science in Laboratory Animals) of the Faculty of Medical Sciences of Unicamp, Campinas, SP, were used in several experiments. These animals had to fast for 12 h before the experiments, and were allowed free access to water. The animals were housed in polyethylene boxes with a capacity to accommodate 5 rats or 10 mice, in an acclimatized room [22±2°C, 55±5% relative humidity (RH)], with periods of light and darkness of 12 h each, automatically controlled. The experimental procedures and use of animals was approved by the Animal Experimentation Ethics Committee of UFPA (Process MED 010/2008) in accordance with the National Institute of Health Guide for the Care and Use of Laboratory Animals.

**Drugs, chemicals and dose used**

For the accomplishment of the experiments, the dose of acetylbergenin was based on the ED50 of 6.8 mg/kg previously determined by Borges et al. (2011). Acetylbergenin was dissolved in 0.2 mL of 2% DMSO (Sigma Chemical Co., USA) and 5% Tween-80 solution (Merck, Brazil). Negative control groups received the same solution used to solubilize the substance acetylbergenin. The drugs used in the experiments were: dexamethasone (0.5 mg/kg, MSD Co., Brazil), indomethacin (5 mg/kg, MSD Co., Brazil), acetylsalicylic acid (100 mg/kg, Bayer, Brazil), and cyproheptadine hydrochloride (Chemical Co., USA) were dissolved and diluted in 0.9% physiological solution. Croton oil (2.5%, Sigma Chemical Co., USA) was solubilized in acetone (Synth, Brazil). The total volume of solution administered orally was 0.25 mL for mice and 0.5 mL for rats.

**Croton oil-induced dermatitis**

The method described by Tubaro et al. (1985) was used in this experiment. Cutaneous inflammation was induced in several groups of mice by applying 0.1 mL (1 mg/paw) of croton oil solution in acetone on the surface of the right ear. The same volume of acetone was applied to the left ear. One hour before the application, three groups of mice (n=10/group) were orally treated with acetylbergenin (6.8 mg/kg, 0.25 mL), vehicle (0.25 mL, 2% dimethyl sulfoxide (DMSO) and 2% Tween-80 in distilled water, control group, or acetylsalicylic acid (100 mg/kg, 0.25 mL). Six hours later, the mice were submitted to euthanasia and the anti-inflammatory effect was evaluated. Samples of 6 mm in diameter were extracted using a punch biopsy, and the weight difference between the samples of the control ear (left) and the croton oil-treated ear (right) was calculated. The results obtained are represented in weight (mg).

**Carrageenan-induced paw edema in rats assay**

Edema was induced by intraplantar injection of 1% carrageenan (100 µg/paw, 0.1 mL, Sigma Co., USA) into the right paw of Mac Coy rats (n = 5/group). A saline sample of equal volume was injected in the left paw (0.1 mL). The distinct experimental groups were treated with vehicle (2% DMSO and 2% Tween-80 in distilled water, negative control, 0.5 mL), acetylbergenin (6.8 mg/kg, 0.5 mL), or indomethacin (positive control, 10 mg/kg, 0.5 mL), and after60 min they received intraplantar injections of carrageenan in the right hind paw and saline in the left hind paw. A digital pachymeter (Zaas Precision, Mitutoyo Co., Japan) was used to
detemine the paw diameter at 1 h intervals after stimulus application over 6 h. The amount of edema was calculated by subtracting the measured volume of the paw injected with saline from the measured volume of the paw injected with carrageenan.

Dextran-induced paw edema in rats assay

The paw edema was induced by dextran in rats, following the method described by Carvalho et al. (1999). The Mac Coy rats were randomly divided into three groups (n = 5/group). A volume of 0.1 mL of 1% dextran (100 µg/paw, 0.1 mL, Sigma Co., USA) solution was injected on the plantar surface of the right hind paw in rats pretreated 60 min earlier with vehicle (2% DMSO and 2% Tween 80 in distilled water, 0.5 mL, control group, p.o.), acetylbergenin (6.8 mg/kg, 0.5 mL, p.o) or the reference drug cyproheptadine (10 mg/kg, 0.5 mL, p.o.). The inflammation was quantified by measuring the volume (mL) displaced by the paw using a digital pachymeter (Zaa Precision, Mitutoyo Co., Japan) at 0, 30, 60, 90, and 120 min after dextran injection. Results were expressed as variation in volume (mL) between the right and left paws at each time.

Carrageenan-induced peritonitis in rats

Different groups of rats (n=8/group) were treated with acetylbergenin (6.8 mg/kg, p.o., 0.5 mL), dexamethasone (0.5 mg/kg, p.o., 0.5 mL) or vehicle (2% DMSO and 2% Tween-80 in distilled water, p.o., 0.5 mL) administered 30 min before the stimulus injection (100 µg/mL carrageenan, 4 mL intraperitoneally). All groups were given an injection of carrageenan and cell migration was evaluated 4 h later. The cell migration analysis was based on the methods described by Carvalho et al. (1999). The results obtained in the differential count were expressed as the number of neutrophils per milliliter of exudates.

Stress-induced acute gastric ulcer

Ulcers were induced according to the method described by Basile et al. (1990). Wistar rats were fasted with free access to water for 24 h and were further treated with vehicle (2% DMSO and 2% Tween-80 in distilled water 0.5 mL, p.o), acetylbergenin (6.8 mg/kg, 0.5 mL, p.o), and indomethacin (10 mg/kg, 0.5 mL, p.o). Groups of five animals each were treated and 30 min later, each animal was kept for 17 h in a contender tube, which was immersed vertically until the water reaching the neck region of the animal in a tank with current water at 25°C. Furthermore, the rats were submitted to euthanasia by CO2 inhalation. Their stomachs were immediately excised, opened by cutting along the greater curvature, and the inner wall was examined for lesions using a binocular stereomicroscope with a magnification of 10× (Nikon SMZ-10). The number and the severity of the acute lesions were enumerated and graded as follows: light (1+) = presence of hyperemia and single mucosal punctiform hemorrhages (petechiae); moderate (2+) = presence of submucosal hemorrhagic lesions with small erosions; severe (3+) = presence of hemorrhagic edges with severe erosions and some invasive lesions. A lesion index was determined following the formula reported by Basile et al. (1990).

Statistical analysis

Results were expressed as mean ± standard error of mean (SEM). Statistical analysis was performed using Student’s t-test and analysis of variance (ANOVA), followed by Student-Newman-Keuls. A value of p<0.05 was considered as statistically significant. The analysis was performed using a GraphPad Prism 5.0 program.

RESULTS

Bergenin and acetylbergenin

Compounds 1 and 2 (Figure 1) were identified as bergenin and acetylbergenin, respectively, by the aid of 1H-1H, 1H-13C COSY, DEPT, and HMBC spectra, and by comparison of its NMR spectral data with those related to the literature (Ramaiah et al., 1979; Borges et al., 2011).
Croton oil-induced dermatitis

Pretreatment with acetylbergenin (6.8 mg/kg, p.o.) inhibited 75.42% of the ear edema formation induced by croton oil injection (p<0.001) when compared with the control group. This inhibition of the edematogenic process was similar to that observed with the group treated with acetylsalicylic acid 100 mg/kg (positive control) decreasing the inflammatory process by 78.53% (Figure 2).

Carrageenan-induced paw edema in rat

Carrageenan injection in the animal paws produced a visible and measurable edema, with maximum inflammation observed 4 h after the injection of the inflammatory agent. The group treated with acetylbergenin at a dose of 6.8 mg/kg inhibited the edema formation over the 6 h of the experiment (Figure 3). The maximum edema inhibition was 35.09% (p<0.05, Student's test, and ANOVA).

Dextran-induced paw edema in rats assay

Dextran 1% induced intense paw edema in rats, an effect that reached a maximum level at 1 h after administration and decreased over the subsequent hours. The oral administration with 6.8 mg/kg of acetylbergenin inhibited the dextran-induced edema by 33% (p<0.05). The reference drug cyproheptadine (10 mg/kg, p.o.) significantly (p<0.05) inhibited the dextran-induced paw edema at 30, 60, 90, and 120 min after administration when compared with the control (Figure 4).

Carrageenan-induced peritonitis in rats

In this model of carrageenan-induced leukocyte migration, it was possible to observe an acute inflammatory response in the peritoneal cavity of rats by neutrophil concentration of 3893.25 ×10^6 cells/mL after 4 h. The acetylbergenin (6.8 mg/kg, p.o.) was able to significantly reduce the carrageenan-induced neutrophil count (70%), when compared with the control group treated with distilled water (Figure 5). Treatment of the animals with dexamethasone (0.5 mg/kg, p.o.) 1 h before the experiment, used as a positive control, significantly reduced (94.23%) the cell migration.

Stress-induced acute gastric ulcer

In the stress ulcer experiment, the animals treated with indomethacin (10 mg/kg, p.o) produced more lesions when compared with those treated with acetylbergenin at a dose of 6.8 mg/kg (p.o) (Table 1). Acetylbergenin at a dose of 6.8 mg/kg has revealed significant effect with a ulcer index of 10.08 and protection of 78.55% when
Figure 3. Effect of the p.o. administration of acetylbergenin (6.8 mg/kg), indomethacin (5 mg/kg) and only vehicle (2% DMSO and 2% Tween-80 in distilled water) on rat paw edema, induced by the intraplantar injection of carrageenan (1000 µg/paw). The data is expressed as mean±SEM of five animals, *p<0.05, compared to the control group, Student's "t" test.

Figure 4. Effect of the p.o. administration of acetylbergenin (6.8 mg/kg), cyproheptadine (10 mg/kg) and control (2% DMSO and 2% Tween-80 in distilled water) on rat paw edema induced by the intraplantar injection of dextran (1000 µg/paw). The data is expressed as mean±SEM of five animals; *p<0.05, compared to the control group, Student's "t" test.
**Figure 5.** Effect of the administration (p.o.) of acetylbergenin (6.8 mg/kg) and dexamethasone (0.5 mg/kg), on the migration of neutrophils to the peritoneal cavity in rats induced by 3 mL of carrageenan (100 µg/mL). The bars represent the mean±SEM of the number of neutrophils (n=8/group); **p< 0.01 and ***p< 0.001, when compared to control (Student Newman-Keuls multiple comparison test).

Table 1. Effect of oral administration of control (2% DMSO and 2% Tween-80 in distilled water), acetylbergenin (6.8 mg/kg) and indomethacin (10 mg/kg) on the incidence of gastric lesions of rats produced by stress.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number</th>
<th>Dose (mg/kg)</th>
<th>Lesion numbers</th>
<th>Ulcer index</th>
<th>Curative ratio (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>5</td>
<td>-</td>
<td>0.6±1.34 0.4±0.89 0.6±0.40</td>
<td>3.2</td>
<td>-</td>
</tr>
<tr>
<td>Acetylbergenin</td>
<td>5</td>
<td>6.8</td>
<td>6.8±1.39 9.2±2.15 8.4±2.29</td>
<td>10.08</td>
<td>78.55***</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>5</td>
<td>10</td>
<td>16±3.50 13.6±5.73 32.6±5.73</td>
<td>47</td>
<td>-</td>
</tr>
</tbody>
</table>

***P<0.001 when compared with indomethacin, Student’s t- test and ANOVA.

compared with indomethacin group (p<0.001).

**DISCUSSION**

This study aimed to investigate the anti-inflammatory and antiulcerogenic activities of acetylbergenin using various experimental models in vivo. Acetylbergenin was extracted by acetylation of bergenin, according to Borges et al. (2011). It is well known that several plants in nature comprise a huge reservoir of bioactive molecules that can be developed as new chemical entities, analogs, derivatives, and synthetic compounds to form a natural product (Rastogi and Rawat, 2008).

Experimental models using carrageenan as an inflammatory agent are widely used to investigate the pathophysiology of the inflammatory response, as well as to characterize the novel anti-inflammatory drugs (Tobacman, 2001). Carrageenan induces a measurable local inflammatory response. This model of paw edema is most frequently used to evaluate the effects of anti-inflammatory drugs. This model presents two inflammatory phases and a third, uncharacteristic one. In the first hour after the carrageenan injection, an increase in vascular permeability mediated by histamine and serotonin is observed. In the second hour, the permeability increase is caused by kinines. In the third hour, the increase of vascular permeability occurs due to prostaglandin action (Perazzo et al., 2005).

The data presented in this study revealed that pretreatment of the animals with acetylbergenin at a dose of 6.8 mg/kg, 1 h prior to the intraplantar injection of carrageenan, inhibited the development of paw edema at all evaluation times; however, this inhibition was higher during the second and third peaks (2 and 3 h), revealing the participation of prostaglandins in the third hour. Indomethacin (10 mg/kg, p.o.), considered as a nonspecific cyclooxygenase inhibitor, also significantly
reduced the volume of carrageenan-induced paw edema at all evaluation times, compared to the respective negative control used. In order to demonstrate the participation of prostaglandins in carrageenan-induced edema, some authors have confirmed that pretreatment with aspirin, a nonsteroidal anti-inflammatory drug, promotes endogenous prostaglandin and edema reduction, whereas administration of high doses of prostaglandin E2 (PGE2) or prostacyclin elicited an increase in paw edema (Lewis et al., 1975; Vane and Botting, 1987).

Another phlogistic agent used in the present study was dextran. This substance is a high molecular weight polysaccharide that induces an anaphylactic reaction, characterized by extravasation and formation of edema with little protein and few neutrophils, besides the degranulation of mast cells and subsequent release of histamine and serotonin (Vinegar et al., 1969). Thus, it was possible to observe that in the dextran-induced edema, oral administration of 6.8 mg/kg of acetylbergenin inhibited the edema at the initial stage (1 and 2 h), where the degranulation of inflammatory cells occurred with a release of biogenic amines, serotonin, and histamine.

Swarnalakshmi et al. (1984) reported the anti-edematogenic activity of bergenin, with a dose dependent inhibition in the third hour, with 44.1, 53.6, and 65.5% inhibition at oral doses of 60, 120, and 240 mg/kg, respectively; however, considering this data, it is possible to verify that acetylbergenin was more effective at an oral dose of 6.8 mg/kg, since at this dose it was able to cause 47% edema inhibition induced by carrageenan in the third hour besides being significant in other instances.

Acetylbergenin activity on leukocyte migration was studied in the carrageenan-induced peritonitis model in rats. Oral administration of acetylbergenin (6.8 mg/kg) inhibited neutrophil cell migration by 70%, following the profile similar to that of dexamethasone which caused 94.23% inhibition. This model of acute inflammation allows the quantification of leukocytes that migrate to the peritoneal cavity under the action of chemotactic agents, mainly leukotrienes LTB_{4} (Bastos et al., 2001).

Therefore, in general, the initial process of the acute inflammatory response is characterized by the increase of neutrophils in the circulating blood, being the first line of physiological defense, followed by lymphocytes and monocytes (Male, 2003). The mode of action of carrageenan in inducing the leukocyte migration may be a result of synergism between PGE2, LTB_{4}, and other potent chemotactic agents such as complement (C5a) and interleukins (IL-8), promoting vasodilation, plasma exudation, and leukocyte accumulation in the lesion sites (Thomazzi et al., 2009). Hence, it is possible that non-steroidal anti-inflammatory drugs (NSAIDs), by inhibiting the synthesis of vasodilatory PGE2, promote blood flow reduction by compromising the leukocyte migration to the area of inflammatory reaction (Almeida et al., 1980). The results suggest that the anti-inflammatory activity of acetylbergenin is related to the biosynthesis of prostaglandins and lipoxygenase products.

While testing dermatitis induced by the topical application of croton oil, the activation of phospholipase A2, releasing arachidonic acid with consequent biosynthesis of leukotrienes and prostaglandins, by cyclooxygenase and lipoxygenase pathways, respectively, was observed. This dermatitis is sensitive to the action of topical anti-inflammatory agents, also responding to the systemic administration of steroidal anti-inflammatory drugs (Tubaro, 1986). Acetylbergenin at a dose of 6.8 mg/kg significantly inhibited (p<0.001) the dermatitis and presented a similar result to the nonsteroidal anti-inflammatory acetylsalicylic acid (100 mg/kg).

On the evaluation of the ulcerogenic effect of 6.8 mg/kg acetylbergenin, the substance produced 78.55% less ulcerative damages. In addition, 1+ and 3+ (hemorrhagic) gastric lesions in animals submitted to stress were significantly reduced by treatment with 6.8 mg/kg of acetylbergenin when compared with indomethacin. These results suggest that, despite having performed significantly on carrageenan edema, however, did not show an ulcerogenic effect such as indomethacin, which is a nonspecific cyclooxygenase inhibitor. This effect was like that found for bergenin, at a dose of 30 mg/kg, i.p., when it exerted a non-ulcerogenic effect in rats submitted to the stress-induced gastric ulcer test (Abe et al., 1979).

Gastric cytoprotection is conferred by certain substances, such as prostaglandins. The clinical use of traditional NSAIDs for treating inflammation and pain is often accompanied by adverse gastrointestinal effects. The pharmacological effects of NSAIDs are due to the inhibition of a membrane enzyme called cyclooxygenase (COX), which is involved in the prostaglandin biosynthesis. There are two isoforms, COX-1 and COX-2, which share the same substrates, produce the same products, and catalyze the same reaction using identical catalytic mechanisms, but differ in inhibitor selectivity. The isoform, COX-1, chiefly plays a physiological role in the kidneys and the stomach, whereas COX-2, induces inflammatory conditions and is involved in the production of prostaglandins that mediate pain. Inhibition of COX-1 is responsible for the adverse gastrointestinal and renal effects of NSAIDs, while the inhibition of COX-2 accounts for NSAIDs therapeutic effects. All classical NSAIDs, such as aspirin and indomethacin are nonselective inhibitors of both COX-1 and COX-2, but bind more tightly to COX-1 (Alanazi et al., 2015).

Chung et al. (2001) reported that acetylbergenin, presented greater activity in vivo when compared with bergenin, against the hepatotoxicity in rats. Notably, acetylbergenin is more readily absorbed due to its ability to cross the bilayer of intestinal cell membranes, resulting in an increase in the protective activity after being hydrolyzed into a hydrophilic polyphenol such as norbergenin and bergenin.
Other studies have demonstrated the importance of adding an acetyl radical to a molecule for anti-
edematogenic activity (Carvalho et al., 1999). This may be partially explained by the high specificity of acetylated anti-inflammatory compounds (Souza et al., 2004), such as aspirin, which inhibit prostaglandin synthesis by inactivating COX. Aspirin selectively acetylates the hydroxyl group of a serine residue (Ser 53), among the terminal 70 amino acids of the PGEs enzyme chains. Acetylation leads non-selectively to the irreversible inhibition of isoenzymes (COX-1 and COX-2) (Cerella et al., 2010).

Conclusion
The anti-inflammatory action of acetylbergenin appears to be dependent on COX-2 inhibition. Furthermore, although the anti-inflammatory activity of acetylbergenin is a characteristic of nonsteroidal compounds, it causes little deleterious interference in the gastric mucosa. Based on these results, it was concluded that acetylbergenin has a potential anti-inflammatory activity. The addition of five acetyl groups, from the natural prototype, increased the potential of these results, acetylbergenin has a potential anti-inflammatory activity. Nevertheless, detailed investigations are still necessary in order to study the relationship between the structure and pharmacological activity of acetylbergenin, since its results were quite promising.

CONFLICT OF INTERESTS
The authors have not declared any conflict of interests.

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