GASTROPROTECTIVE EFFECT OF β-LUPEOL: ROLE OF PROSTAGLANDINS, SULFHYDRYLs AND NITRIC OXIDE

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This paper is dedicated to Professor Doctor Rachel Mata for her 60th birthday

ABSTRACT

This investigation evaluated the gastroprotective effect of β-lupeol, isolated from Pseudobombax ellipticum. Gastric mucosal damage was induced in rats by intragastric ethanol (1mL/rat). Rats treated orally with β-lupeol suspended in Tween 80 at 3, 10, 30 and 100 mg/kg, showed 21, 60, 79 and 77 % gastroprotection respectively. The gastroprotection observed at 30 mg/kg for this compound was reverted in rats pretreated with indomethacin (10 mg/kg. s.c.) or N-ethylmaleimide (NEM 10 mg/kg, s.c.), suggesting that the gastroprotective mechanism of this triterpene involves, at least in part, the participation of prostaglandins and endogenous sulfhydryls. The gastroprotective effect of β-lupeol was not affected by the pretreatment with L-NAME (70 mg/kg, i.p.), a nitric oxide (NO)-synthase inhibitor. Carbenoxolone was used as gastroprotective model drug and showed dose dependent gastroprotective effect (26, 44 and 88% of gastroprotection, at 1, 10 and 30 mg/kg, respectively). The participation of prostaglandins, sulfhydryls and nitric oxide was observed in the gastroprotective mechanism of carbenoxolone.

Keywords: gastric ulcer, gastroprotective effect, Pseudobombax ellipticum, β-lupeol, prostaglandins, sulfhydryls.

RESUMEN

En este trabajo se evaluó el efecto gastroprotector de β-lupeol, aislado de la cor- teza de Pseudobombax ellipticum. El daño gástrico se indujo en ratas por la ad- ministración intragástrica de etanol (1 mL/rata). Las ratas tratadas con β-lupeol suspendido en Tween 80 a las dosis de 3, 10, 30 y 100 mg/kg, presentaron 21, 60, 79 y 77 % de gastroprotección respectivamente. La gastroprotección observada
a la dosis de 30 mg/kg de este compuesto fue anulada en ratas pretratadas con indometacina (10 mg/kg, s.c.) o con N-etilmaleimida (NEM, 10 mg/kg, s.c.), indicando que el mecanismo gastroprotector de este triterpeno involucra, al menos en parte, la participación de protaglandinas y grupos sulfhidrilos endógenos. El efecto gastroprotector de β-lupeol no se afectó por el pretratamiento con L-NAME (70 mg/kg, i.p.), un inhibidor de la enzima óxido nítrico (NO) sintasa. La carbadoxolona, utilizada como fármaco gastroprotector de referencia, presentó un efecto gastroprotector dosis-dependiente (26, 44 y 88% de gastroprotección, a las dosis de 1, 10 y 30 mg/kg, respectivamente). Se observó la participación de protaglandinas, grupos sulfhidrilos y óxido nítrico, en el mecanismo gastroprotector de la carbadoxolona.

INTRODUCTION

Gastric and duodenal ulcers affect a considerable amount of people in the world. Ulcer occurs when there is a disturbance of the normal equilibrium caused by either enhanced aggression or diminished mucosal resistance of gastrointestinal tract. Mucosa protects gastrointestinal tract of acid, pepsin, bile, leukocyte infiltration and external substances such as alcohol, caffeine, chilli or certain drugs such as NSAIDs. The defense mechanisms of the gastrointestinal mucosa mainly consist of functional, humoral and neuronal factors. Mucus-alkaline secretions, the phospholipids layer, microcirculation and motility act as functional factor. Prostaglandins (PGs), nitric oxide (NO), lipoxins (LXs) and hydrogen sulfide (H₂S) work as humoral factors and capsaicin sensitive sensory neurons act as neuronal factors (Calatayud et al., 2001; Fiorucci, et al., 2002; Fiorucci, et al., 2005; Tsukimi and Okabe, 2001; Wallace et al., 2007). Various studies have been successful in showing that several triterpenoids and sterols have showed antiulcer activity (Lewis and Hanson 1991; Borrelli and Izzo 2000; Oliveira et al., 2004; Navarrete et al., 2002; Arrieta et al., 2003; Navarrete et al., 2005; Sánchez-Mendoza et al., 2008). The gastroprotective effects of triterpenoids have been studied on ethanol or NSAIDs-induced gastric injury models. These models induce impairment in the mucosal defense process with the consequent gastric damage. The major mechanism of gastroprotection of triterpenoids has been reported by the activations of mucous membrane secretion instead of the inhibition of gastric acid secretion. Chemically, this gastroprotective effect has been referred to the presence of a hydroxyl group free or derivative at position C-3 for sterols and triterpenoids (Oliveira et al., 2004; Navarrete et al., 2002; Arrieta et al., 2003; Navarrete et al., 2005; Sánchez-Mendoza et al., 2008). In continuation with our studies on the gastroprotective effect of triterpenoids (Navarrete et al., 2002; Arrieta et al., 2003; Navarrete et al., 2005; Sánchez-Mendoza et al., 2008), we were interested in the study of the gastroprotective effects of β-lupeol (Lup-20(29)-en-3H-ol), a bioactive pentacyclic triterpene (Figure 1) that occurs across a multitude of taxonomically diverse genera. Besides that, β-lupeol is also found in various edible plants such as olive, fig, mango, strawberry, red grapes and medicinal plants used widely by native peoples of North America, Japan, China, Latin America, and the Caribbean islands (Beveridge et al., 2002; Kakuda et al., 2002; Saleem et al., 2001). β-Lupeol has been shown to exhibit strong anti-inflammatory, antiarthritic, anti-mutagenic and anti-malarial activity both in vitro and in vivo (Saleem et al., 2001) and wound healing activity (Harish et al., 2008). In recent years, β-lupeol was found to have a new property to add to its arsenal: anti-cancer activity.
β-Lupeol has been reported not only to induce differentiation and inhibit the growth of melanoma and leukemia cells but also to inhibit tumor promotion in two-stage mouse skin carcinogenesis and to inhibit growth and induce apoptosis in both prostate and pancreatic cancer (Chaturvedi et al., 2008; Zhang et al., 2009). On the other hand, β-lupeol acetate has exhibited anti-ulcer activity in the Say ulcer model and in the stress-induced ulcer model (Lewis and Hanson, 1991), but there are not studies on the gastroprotective effect of lupeol or other derivatives. Therefore, in the present study we investigated the gastroprotective effect of β-lupeol, isolated from stem bark of *Pseudobombax ellipticum* Kunth Dugand (Bombacaceae), using as an experimental model the inhibition of the ethanol induced ulcers in rats. We also discuss the role of endogenous nitric oxide (NO), sulfhydryls and prostaglandins in the gastroprotection of this triterpene.

**MATERIALS AND METHODS**

**Animals**

All the experiments were performed with male Wistar rats, 55-60 day old, weighing 180-220 g, obtained from Centro UNAM-Harlan (Harlan México, S.A. de C.V.). Procedures involving animals and their care were conducted in conformity with the Mexican Official Norm for Animal Care and Handling (NOM-062-ZOO-1999) and in compliance with international rules on care and use of laboratory animals. The rats were placed in single cages with wire-net floors and deprived of food 24 h before experimentation but allowed free access to tap water throughout. All experiments were carried out using 6 animals per group.

**β-Lupeol**

β-Lupeol was isolated from stem bark of *Pseudobombax ellipticum*. Stem bark of *P. ellipticum* was collected in Tehuetlán, Municipio de Huejutla, Estado de Hidalgo, Mexico in June 2003. A voucher specimen has been deposited in the Herbarium of Universidad Autónoma Chapingo (XOLO200301). The air-dried powdered stem bark (7.45 kg) was extracted with hexane (15 L) under reflux (2 h). The hexane extract was evaporated to dryness in vacuo to yield 136.6 g of crude extract (yield 1.8%). A portion of hexane extract (120 g) was fractionated by open column chromatography by silica gel (1.2 kg) employing hexane and hexane-ethyl acetate (95:5) as eluents, yielding 47 fractions of 200 mL each. From fractions 24-47, eluted with hexane-ethyl acetate (95:5), yielded 7.5 g of crude β-lupeol as white powder. The total of this powder was suspended with 100 mL of 2% carboxymethyl cellulose of low density in water. After 24 h, this mixture was concentrated through an air current at room temperature (approximately 22 °C) to eliminate water. The residue was purified by open column chromatography packed with silica gel (100 g) and eluted with hexane-ethyl acetate (95:5). Fractions 4-17 (25 mL each), gave colorless crystals, which was crystallized from methanol, affords β-lupeol (5.7 g) mp 213-215 °C. EI-MS: m/z (rel int) 426 [M⁺, (100)], 411(26), 393(8), 385 (7), 315(21), 257 (13), 207(78), 204 (18), 189 (80), 135 (61), 109(45), 95(46), 81(36), 55(12). IR (KBr) ν_max 3347, 2943, 1638, 1453, 1379, 880 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 0.760 (3H,s,Me-24), 0.786 (3H,s,Me-28), 0.828 (3H,s,Me-25), 0.943 (2H,s,-27), 0.967 (2H,s,-23), 1.028 (2H,s,-26), 1.680 (3H,s,Me-30), 2.39 (1H,m,H-19), 3.18 (1H,m,H-3), 4.56 (1H,m,H-29a), 4.69 (1H,m,H-29b). ¹³C NMR (75.5 MHz, CDCl₃) δ 38.66 (C-1), 27.37 (C-2), 78.97 (C-3), 38.83 (C-4), 55.24(C-5), 18.28(C-6), 34.23(C-7), 40.78(C-8), 50.38(C-9), 37.12(C-10), 20.80(C-11), 25.08(C-12), 37.99(C-13), 42.79(C-14), 27.40(C-15), 35.54(C-16), 42.97(C-17), 48.24(C-18), 47.95(C-19), 150.96(C-20), 29.80(C-21), 39.97(C-22), 27.96(C-23), 15.36(C-24), 16.10(C-25), 15.94(C-26), 14.52(C-27), 17.97(C-28),
These data were in agreement to those previously reported (Reynolds et al., 1986; Thanakijcharoenpath and Theanphong, 2007).

Drug and dosage
Carbenoxolone (Sigma-Aldrich Co.) was used as gastroprotective model drug (Wan and Gottfried, 1985). The drugs were prepared freshly each time and administered suspended in 0.5% Tween 80 by intragastric route. Control rats received the vehicle (0.5% Tween 80) in the same volume (0.5 mL/100 g) by the same route. N\textsuperscript{-}G-nitro-L-arginine methyl ester (L-NAME), N-ethylmaleimide (NEM) and indomethacin (IND) were purchased from Sigma Chemical Co. USA.

Acute gastric ulcers induced by absolute ethanol
Ulceration was induced according to the method described by Robert (1979), by intragastric instillation of absolute ethanol. Rats were divided into different groups of six animals each. Each group received either vehicle (1 ml/kg), β-lupeol (3-100 mg/kg), or carbenoxolone (1-30 mg/kg) as gastric gavage. Thirty minutes after drug administration, absolute ethanol was given orally to each animal at a dose of 1 ml/rat. Two hours after ethanol administration, the rats were killed in a CO\textsubscript{2} chamber. The stomach and duodenum were dissected out, inflated with 10 mL of 2% formalin, placed in 2% formalin for 15 min to fix both the inner and outer layers. The duodenum was opened along its anti-mesenteric side and the stomach along the greater curvature. The damage area (mm\textsuperscript{2}) was measured under a dissection microscope (X10) with an ocular micrometer. The sum of the area of all lesions in the corpus for each animal was calculated and served as the ulcer index. Gastroprotection (%) was calculated according to: % Gastroprotection = (UIC-UIT)x100/UIC, where UIC is ulcer index in control and UIT is ulcer index in test (Navarrete et al., 1998).

Ethanol-induced gastric mucosal lesions in indomethacin-pretreated rats
In order to investigate the involvement of endogenous prostaglandins in the gastroprotective effects of β-lupeol or carbenoxolone, the animals were divided in groups according to the respective treatment. The control group received a subcutaneous injection of NaHCO\textsubscript{3} (5 mM) in saline solution and the others, an injection of indomethacin (10 mg/kg, dissolved in NaHCO\textsubscript{3}, 5 mM) by the same route (Matsuda et al., 1999). After 75 min, all the animal groups received the respective treatment orally (saline solution, 30mg/kg of β-lupeol or 30 mg/kg of carbenoxolone). Absolute ethanol was given to each animal 30 min after drug administration and the animals were killed 2 h later in a CO\textsubscript{2} chamber. The stomachs were subsequently removed to measure the ulcer index, as described earlier.

Ethanol-induced gastric mucosal lesions in N\textsuperscript{G}-nitro-L-arginine methyl ester-pretreated rats.
To investigate the involvement of endogenous NO in the protective effects of β-lupeol or carbenoxolone, N\textsuperscript{G}-nitro-L-arginine methyl ester (L-NAME, 70 mg/kg dissolved in saline solution) was intraperitoneally injected 30 min before the administration either vehicle, β-lupeol (30 mg/kg) or carbenoxolone (30 mg/kg) through the oral route (Matsuda et al., 1999). Absolute ethanol was given to each animal 30 min later and animals were killed 2 h after the administration of ethanol to measure the intensity of the gastric ulcers. Two control groups (L-NAME-treated and non-L-NAME-treated) were included in this experiment.

Ethanol-induced gastric mucosal lesions in N-ethylmaleimide-pretreated rats
To investigate the involvement of endogenous sulphydryls in the protective effects of β-lupeol or carbenoxolone, N-ethylmaleimide (NEM, 10 mg/kg, dissolved in saline solution) was subcutaneously injected 30
min before the administration either vehicle, β-lupeol (30 mg/kg) or carbenoxolone (30 mg/kg) through the oral route (Matsuda et al., 1999). Absolute ethanol was given to each animal 30 min later and animals were killed 2 h after the administration of ethanol to measure the intensity of the gastric ulcers. Two control groups (NEM-treated and non-NEM-treated) were included in this experiment.

**Statistics**

Data are presented as the mean ± SEM from 6 rats per group. Statistically significant differences between the treatments were tested by Kruskal-Wallis test (non parametric one-way analysis of variance) followed by Dunn’s multiple comparison test. Probability (p) values less than 0.05 were considered significant.

**RESULTS**

β-Lupeol administered orally reduced the ethanol-induced gastric hemorrhagic lesions, became significant (p<0.05) from 10 to 100 mg/kg compared with responses obtained to control group (Fig 2A). The percentage inhibition of ulcers (% gastroprotection) obtained with 30 mg/kg of β-lupeol (79.3 ± 7.6 % of gastroprotection) was similar to that obtained with 100 mg/kg (77.2 ± 7.5 % of gastroprotection) of this compound. Carbenoxolone showed

**Figure 1.** Structure of β-lupeol.

**Figure 2.** Effect of different doses of (A) β-lupeol (3-30 mg/kg) and (B) carbenoxolone (1-30 mg/kg) administered orally on gastric hemorrhagic lesions induced by absolute ethanol (1ml/rat) in rats. Bars represent the mean ± S.E.M. (n= 6). * p<0.05, significantly different from the respective control; Dunn’s multiple comparison test after Kruskal-Wallis test.
its maximum % gastroprotection (88.4 ± 5.4%) at 30 mg/kg.

The ulcer indexes of the animals treated with 10 mg/kg of indomethacin (101.6 ±13.1 mm², Fig 3A), 10 mg/kg of NEM (125.2 ±11.0 mm², Fig 3B) or 70 mg/kg of L-NAME (98.2 ±9.6 mm², Fig 3C), were not significantly (p>0.05) different compared with their respective controls treated only with saline solution (132.6 ±16.8 mm², 93.5 ±12.0 mm² and 84.2 ±12.3 mm², respectively). It is very well recognized that these doses inhibit prostaglandins synthesis, blockade the endogenous sulfhydryls and inhibit nitric oxide synthase (NOS) respectively, but do not cause ulcers (Matsuda et al., 1999; Arrieta et al., 2003).

Pretreatment with 10 mg/kg of indomethacin attenuated the gastroprotective effect of both β-lupeol (30 mg/kg) and carbenoxolone (30 mg/kg) (Fig 3A). The ulcer index obtained in the animals treated with β-lupeol (105.8 ±12.1 mm²) and carbenoxolone (95.3±14.2 mm²) were not significantly (p>0.05) different compared with the indomethacin -pretreated controls (101.6 ±13.1 mm²), whereas the values for β-lupeol and carbenoxolone in indomethacin -pretreated rats were significantly (p<0.05) higher than the ulcer index values obtained for the same drugs in non- indomethacin -treated rats (16.5±6.1 mm² and 30.0±14.2 mm², respectively) (Fig 3A).

Pretreatment with 10 mg/kg of NEM abolished the gastroprotective effect of both β-lupeol (30 mg/kg) and carbenoxolone (30 mg/kg) (Fig 3B). The ulcer index obtained in the animals treated with β-lupeol (107.5 ±11.5 mm²) and carbenoxolone (83.3±14.0 mm²) were not significantly (p>0.05) different compared with the NEM -pretreated controls (125.2 ±11.0 mm²), whereas the values for β-lupeol and carbenoxolone in NEM -pretreated rats were significantly (p<0.05) higher than the ulcer index values obtained for the same drugs in non- NEM -treated rats (16.0±6.0 mm² and 29.5±14.5 mm², respectively) (Fig 3B).
β-lupeol (30 mg/kg) administered orally, produced inhibition of ethanol-induced hemorrhagic lesions in L-NAME (70 mg/kg)-pretreated animals. The ulcer index obtained for β-lupeol -treated rats was 53.5 ±7.0 mm². This value was significantly (p<0.05) different compared with the L-NAME-pretreated controls (98.2±9.6 mm²), whereas the value for 30 mg/kg carbenoxolone (70.2 ±13.1 mm²) was not significantly different (p>0.05) from the control value (Fig 3C). There was significant difference (p<0.05) between L-NAME-treated and non-L-NAME-treated rats for carbenoxolone (70.2 ±13.1 mm² versus 29.8 ±14.0 mm², respectively), but not for β-lupeol (43.5 ±7.0 mm² versus 15.8 ± 6.6 mm², respectively) (Fig 3C).

DISCUSSION

The present study revealed clearly that β-lupeol exerted gastroprotective effect in the ethanol-induced gastric hemorrhagic lesions model (Figure 2). In the recent past, an important number of works have described the gastroprotective effects of a variety of triterpenes, both aglycons as glycosides; these kind of natural products have showed gastroprotective effects on the damage induced with ethanol or non steroidal anti-inflammatory drugs (NSAIDs) in various experimental procedures. Thousands of triterpene structures have been reported till date with hundreds of new derivatives discovered each year. These compounds occur commonly and are found in fruits, vegetables and other parts of several medicinal plants. There are at least 4000 known triterpenes most of which occur freely but others occur as glycosides or in special combined forms (Juri, 2003). Pentacyclic triterpenes have a wide spectrum of biological activities and some of them may be useful even in medicines. These include the pentacyclic lupane-type triterpenes which are represented by a diverse assemblage of bioactive natural products. Among this class of compounds, β-lupeol occurs across a multitude of taxonomically diverse genera. The gastroprotective effect demonstrated for β-lupeol is a new activity to add to its arsenal of biological activities (Chaturvedi et al., 2008). The alone antecedent on the gastroprotective effect of β-lupeol correspond to the antiulcer activity of β-lupeol acetate in the Say ulcer model and in the stress-induced ulcer model (Lewis and Hanson, 1991). On the other hand, it has been proposed that a hydroxyl group at position C-3 (free or derivative) is necessary for sterols and triterpenoids to exhibit antiulcer activity (Navarrete et al., 2002). In this regard, both β-lupeol as its acetate, fulfill with this characteristic.

It is well known that ethanol produces gastric mucosal damage within 1-3 min of its instillation into the gut and lasts for more than 2 h by causing areas of focal hypereemia and hemorrhage (Chandranath et al., 2002). Moreover, intragastric administration of ethanol increases vascular permeability and vascular damage occurring in capillaries near the luminal surface and not in the deeper muscularis mucosa, which indicates a role for impaired blood flow in the genesis of ethanol-induced gastric lesions (Chandranath et al., 2002).

Integrity of the gastric mucosa requires continuous generation of prostacyclin (PGI2) and prostaglandin E2 (PGE2) (Atay et al., 2000). Suppression of prostaglandin synthesis by NSAIDs results in increased susceptibility of the mucosa to injury (Laine et al., 2008). When gastric mucosal defense is compromised, exogenous noxious agents (e.g. ethanol, NSAIDs), together with HCl and pepsin, penetrate into the mucosa and damage the mucosa microvasculature. This damage produces reduction in oxygen and nutrient delivery resulting in the release of pro-inflammatory and vasoactive mediators (serotonin, endothelin, leukotriene C4, and platelet activating factor) that in turn exaggerate ischemic necrosis (Tarnawski
and Hollander, 1987). Pretreatment with indomethacin (10 mg/kg) resulted in a completely abolishment of gastroprotective effect of β-lupeol (30 mg/kg) and carbenoxolone (30 mg/kg) (Figure 3A). These findings suggest that endogenous prostaglandins play an important role in the gastroprotective effect of β-lupeol.

Ethanol causes depletion of the gastric levels of proteins, nucleic acids, NP-SH (non-protein sulfhydryl groups) and an increment on MDA (malondialdehyde) levels and decrement of antioxidants substances (Zamora-Rodríguez et al., 2007). Moreover, it has been described that depletion of NP-SH groups by ethanol increases the content of free radicals mediate tissue injury by stimulating lipid peroxidation and membrane damage (Al-Shabanah et al., 2000). Blocking non-protein-SH groups with NEM resulted in a completely abolishment of gastroprotective effect of β-lupeol (Figure 3B). These results suggesting a role more evident of endogenous non-protein-SH group on the gastroprotective effect of this triterpene. The relationship between the effect of blocking NP-SH and the reduction or abolishment of the gastroprotective effect of several triterpenoids (Navarrete et al., 2005; Arrieta et al., 2003; Matsuda et al., 1999; Sánchez-Mendoza et al., 2008) is unclear. However the possibility that triterpenoids act as sulfhydryl-containing agents through the stimulation of the release of gastric mucin glycoproteins in a synergistic manner with NP-SH is not discarded (Salim, 1992). But it is necessary the experimental demonstration of this suggestion.

NO seems to have low participation in the mechanism of gastroprotection of β-lupeol, because the gastroprotection of this compound was reduced but not significantly by the pretreatment with L-NAME, an inhibitor of NO synthesis (Figure 3C). However, the gastroprotective effect of carbenoxolone was reversed by the pretreatment with L-NAME (Figure 3C).

The results obtained here for carbenoxolone are in agreement with those previously reported (Wan and Gottfried 1985; Arrieta et al., 2003). As it is known, in the gastroprotective mechanism of carbenoxolone are intensively involved the prostaglandins and partially nitric oxide and sulfhydryls (Arrieta et al., 2003).

Ethanol-induced gastric injury is related with an inflammatory process (Tarnawski and Hollander, 1987); higher levels of tumoral necrosis factor- alpha (TNF-α) contributes to the pathogenesis of ethanol-induced gastric damage (Ferraz et al., 1997). In addition, it has been reported that β-lupeol decreases pro-inflammatory cytokines such as TNF-α in macrophages (Fernández et al., 2001). Therefore, it is not discarded the possibility that the gastroprotective effect observed here for β-lupeol may be related with a decrement in the levels of gastric TNF-α on ethanol-induced gastric damage in the rat. However, more studies needs to be done to elucidate this suggestion on the gastroprotective mechanism of this triterpene.

Finally, vegetables, fruits, dietary fiber, and certain micronutrients apparently seem to be protective against ulcer, whereas fat, excessive calories and alcohol seem to increase the ulcer risk, therefore the results found here for the triterpene β-lupeol together with the reports on the gastroprotective activity of an important number of other triterpenes, might play an important role in establishing a relationship between phytosterols and triterpenes intake in vegetarian diets and the protection gives to the development of gastric ulcers. In a similar manner as it has been suggested the protective effect of vegetables, fruits and dietary fiber against carcinogenesis at various sites, including the oral cavity, esophagus, stomach, colon/rectum, lung, breast, and prostate (Chaturvedi et al., 2008).
CONCLUSION

In this work it was demonstrated the gastroprotective activity of β-lupeol. The endogenous prostaglandins and non-protein sulfhydryl groups play an important role in the gastroprotective mechanism of this triterpene on the ethanol-induced gastric lesions. These results highlight the importance of triterpenes contents in edible and medicinal plants. Acknowledgements

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