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Anti-ulcer, Analgesic and Antioxidant Activities of Aqueous Extract of *Foeniculum vulgare* Mill Seeds

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ABSTRACT

Foeniculum vulgare Mill, known as fennel, is a medicinal plant of the Apiaceae family, widely used in traditional Algerian medicine. The aim of this study was to estimate the polyphenols and flavonoids content and to evaluate the antioxidant, the analgesic and the antiulcer activities of aqueous extract of *F. vulgare* seeds. Quantitative determination of total polyphenols and flavonoids revealed that this extract contained 551.45±0.010 mg gallic acid equivalent/g of dry extract and 284.83±0.008 mg quercetin equivalent/g of dry extract respectively. The study of the gastroprotective effect showed that this extract is able to protect the stomach against lesions induced by 70% ethanol. The percentages of protection were 55.54±6.99 and 71±3.09% for the 200 and 400 mg/kg doses respectively. The study of the analgesic activity indicated that the aqueous extract of *F. vulgare* reduced the pain induced by acetic acid (0.6%) with an inhibition rate of 47.89% and 68.65% for doses of 200 and 400 mg/kg respectively. Free radical 2,2-diphenyl-1-picrylhydrazyl and iron chelation tests were applied to evaluate the *in vitro* antioxidant activity. The free radical scavenging activity of *F. vulgare* extract against 2,2-diphenyl-1-picrylhydrazyl radicals revealed an IC_{50} value of IC_{50}=30.91±0.49 mg/mL in comparison with gallic acid (0.038±0.0002 mg/mL). The iron chelating test showed that the extract had a high capacity for iron chelating, which was estimated at 0.346±0.003 mg/mL in comparison with the chelating reference agent, ethylene diaminetetraacetic acid.

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Introduction

The history of the use of medicinal and aromatic plants dates back to the beginnings of humanity. Our ancestors used natural substances they could find in nature to relieve, heal their sufferings, illnesses, and wounds. This type of approach has survived in traditional medicinal use until today, since nearly 80% of the world's population still depends on medicinal plants in their medicines (Màthé, 2015; Korkmaz et al., 2021). Medicinal plants have become "industrial products" with new concepts such as phytotherapy, aromatherapy and veterinary medicinal uses (Sevindik et al., 2017; Pehlivan et al., 2021). The medicinal values of these plants are due to the presence of active compounds that produce physiological actions in the human and animal body. Some of the important bioactive compounds found in medicinal plants are: secondary metabolites (polyphenols, flavonoids, tannins…) (Kına et al., 2021; Uysal et al., 2021).

Due to the strong association between oxidative stress, aging and disease, there is increasing interest in the biomolecular effects of medicinal plants that may be related to the antioxidant action (Benzie and Wachtel-Galor, 2011; Mohammed et al., 2020; Akgül et al., 2022). Virtually every disease examined to date involves free radicals. Although in most cases free radicals are a secondary cause of the disease process, in some cases the causality is established for free radicals.

Fennel or *F. vulgare* Mill is one of the oldest spice plants that grow widely in arid and semi-arid regions and due to its economic importance and use in the pharmaceutical industry; it is the one of the most important medicinal herbs. This plant has an anti-inflammatory, antispasmodic, antiseptic, carminative, diuretic and analgesic effect and is effective in the treatment of gastrointestinal and neurological disorders (Kooti et al., 2015).

Materials and Methods

Plant Material

F. vulgare seeds were purchased from the herbalist in Setif region (North of Algeria). The plant was powdered and stored until use.

Animal Material

Female Albino Wistar mice weighing 20 to 30 g used in this study were obtained from Pasteur Institute of Algiers (Algeria). The experimental animals were used after an adaptation period at room temperature. The animals were divided into groups and had free access to water and food.

Preparation of Aqueous Extract

The aqueous extract was prepared according to method used by Markham (1982). 50 g of powdered *F. vulgare* seeds were extracted with 500 mL of boiling distilled water for 20 minutes. The mixture was filtered and concentrated to obtain crude aqueous extract.

Determination of Total Polyphenols

For the determination of the content of total polyphenols in the aqueous extract of *F. vulgare*, the Folin-Ciocalteu technique according to Lie et al. (2007) was adopted. To carry out this procedure, add 500 µL of Folin-Ciocalteu reagent (diluted 10 times) to 100 µL of sample (extract) or gallic acid (standard). After 4 minutes, 400 µL of 7.5% sodium carbonate solution (Na_2CO_3) were added. After an incubation period (90 minutes) in the dark and at room temperature the absorbance of samples was read at 765 nm. The results were expressed in milligrams of gallic acid equivalent per gram dried extract (mg GAE/g DE).

Determination of Total Flavonoids

The dosage of flavonoids was carried out according to the method of aluminum trichloride ($AlCl_3$) (Bahorun et al., 1996). 0.5 mL of 2% $AlCl_3$ was added to 0.5 mL of the extract or quercetin. The absorbance was read after 10 minutes of incubation at 430 nm. The results were expressed in milligrams of quercetin equivalent per gram dried extract (mg QE /g DE).

Ethanol Induced Gastric Ulcer

The gastro-protective effect of *F. vulgare* aqueous extract was determined using the ulcer induction model with ethanol (70%). The mice were deprived of food for 18 hours and had free access to water up to one hour before the experience. Animals were placed in individual cages to avoid coprophagia and divided into four groups: negative control group, positive control group (ranitidine 5 mg/kg), extract (200 and 400 mg/kg) groups. Water, extract and ranitidine were administered intragastrically by gavage. One hour later, 70% ethanol was administered orally. Each animal was sacrificed by cervical dislocation thirty minutes after the administration of the ethanol and the stomach was removed and opened along the great curvature and rinsed with NaCl then spread on a cork plate to determine the surface of the lesions using the software (Image J). Results were expressed as protection percentage.

Acetic Acid-Induced Abdominal Constrictions

Analgesic activity was evaluated by writhing test. The acetic-acid writhing test was performed using the reported procedure (Aoki et al., 2006). Four groups of mice were administered by gastric gavage with 200 and 400 mg/kg of aqueous extract of *F. vulgare* seeds, 10 mg/kg sodium diclofenac as positive control and distilled water as negative control. After one hour, the animals were administered with intraperitoneal injection of 0.6% acetic acid. Then the count of abdominal constrictions of animals during 25 minutes after acetic acid injection was reported and the percentage protection against abdominal writhing was used to assess the degree of analgesia.

Evaluation of the Antioxidant Activity

DPPH radical scavenging test

The antioxidant activity of the aqueous extract of *F. vulgare* seeds and the standard antioxidants (gallic acid and BHT) was determined by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) test according to the method described by Sanchez-Moreno et al. (1998). 50 µL of different concentrations of the extract or standards antioxidant was mixed with 1250 µL of 0.004% DPPH solution. The reaction mixture was left in the dark at room temperature for 30 minutes and the absorbance was measured at 517 nm. The results were expressed as IC_{50} (mg/mL).

Inhibition percentage (%) of free radical DPPH was calculated according to the following formula:

$$I\ (\%) = 100\ (A_0 - A_1)\ /A_0$$

A_0: Absorbance of the blank.
A_1: Absorbance of the sample.

Iron chelating power

The effect of seeds extract on Fe^{2+}-ferrozine complex formation was studied in order to find the *in vitro* iron chelating activity. The chelating capacity of iron was determined according to the method of Lie et al. (2007) which is based on the inhibition of the formation of the Fe^{2+}-Ferrozine complex after treatment of the samples with Fe^{2+} ions. 250 µL of the ethylene diaminetetraacetic acid (EDTA) or extract was initially mixed with 50 µL of 0.6 mM $FeCl_2$ and 450 µL of methanol. After 5 minutes, 50 µL of 5 mM ferrozine were added to the reaction medium. The mixture was shaken vigorously and left to react for 10 minutes at room temperature. The absorbance was measured at 562 nm. Chelating activity was expressed as a percentage using the equation below:

$$\text{Chelating activity}\ (\%) = 100\ (A_0 - A_1)\ /A_0$$

A_0: Absorbance of the control.
A_1: Absorbance of the sample.

Statistical Analysis

The results were expressed as the mean ± standard error of mean. One-way analysis of variance followed by the Tukey test was performed to assess differences between groups. The values of $P \leq 0.05$ were considered statistically significant. Statistical analyses were performed with the software GraphPad Prism 7®.

Results and Discussion

Polyphenols and Flavonoids Content

The contents of polyphenols and flavonoids in the aqueous extract were found to be 551.45±0.010 mg GAE/g DE and 284.83±0.008 mg QE/g DE respectively. In this study, flavonoids represent 50% of total polyphenols. Anwar et al. (2009) revealed the contents of polyphenols and flavonoids in the methanolic extract of *F. vulgare* of 0.627±0.183 mg GAE/g DE and 0.374±0.128 mg equivalent of catechin/g DE respectively. These results are in agreement with those obtained by Chatterjee et al. (2012) who found that the aqueous extract of fennel seeds contains the highest amount of phenols in comparison with the methanolic extract. The quantity of phenolic compounds in the extracts essentially depends on their origin (Ebrahimzadeh et al., 2008). Mariangela et al. (2008) found a significant difference in total phenol and flavonoid content in fennel seeds from different countries. Similarly, the variability of the levels found between the different origins can be attributed to several factors such as the degree of maturation of seeds, the climate and the growing conditions of the plant (Sayed Ahmed, 2018; Benabdallah et al., 2020).

Anti-ulcer activity

The mice of the negative control group having received ethanol, developed characteristic gastric lesions in the glandular part of the stomach, represented by ulcerations and redness of the mucosa (Figure 1) with an optimal percentage of lesions of 25.31±6.98% (Figure 2). Ethanol is a commonly used ulcerogenic agent; it produces severe gastric bleeding lesions. The mechanism of ethanol-induced gastric injury is varied including depletion of gastric mucus content, impaired mucosal blood flow and mucosal cell injury. In addition, ethanol-induced gastric mucosal damage is associated with overproduction of free radicals, leading to increased lipid peroxide content. The increased content of lipid peroxide and oxygen-derived free radicals leads to marked changes in cell levels and causes membrane damage, cell death, erosion and epithelial damage (Birdane et al., 2007). A significant reduction ($P \leq 0.05$) of lesion surfaces, in the group treated with ranitidine (5 mg/kg), compared to the negative control group with a percentage of lesions of 4.6±1.83% which gives a protection percentage of 81.81±7.22%. The treatment of mice with the aqueous extract of *F. vulgare* at two doses (200 and 400 mg/kg) showed the presence of a significant difference ($P \leq 0.05$) between the negative control group and the groups treated with the extract whose lesion percentages were 11.25±1.77 and 7.34±0.78% respectively. A significant percentage of protection was observed in the group treated with the 400 mg/kg dose (71±3.09%). Statistical analysis showed that there is no significant difference between the group treated with the 400 mg/kg dose and the positive control ($P > 0.05$), while the 200 mg/kg dose of the extract gives the lowest inhibition of lesions with a percentage protection of 55.54±6.99%.

These results demonstrated that the aqueous extract of *F. vulgare* can be considered as a powerful gastro-protector. Indeed, the work of Birdane et al. (2007) showed that the pretreatment of rats with the aqueous extract of *F. vulgare* gives a good protective effect against gastric ulcer induced by 80% ethanol with a percentage inhibition of 68.2% at a dose of 300 mg/kg. This confirms our results of the efficacy of the aqueous extract of the seeds of *F. vulgare* against gastric ulcer. The present study revealed that this extract had antioxidant properties that may be, at least partially, one of the possible mechanisms by which *F. vulgare* ameliorated ethanol-induced gastric injury. Additionally, flavonoids are also known to possess anti-ulcer activity. They protect the gastric mucosa against various ulcerogenic agents via several mechanisms of action, mainly the antiradical properties, the trapping of free radicals, the increase in the production of mucus, the anti-secretory action, and the inhibition of growth of *Helicobacter pylori* (Sumbul et al., 2011). On the other hand, polyphenols have the ability to prevent the migration of neutrophils to the epithelium of the stomach, these cells play an important role in reducing blood flow, through the formation of the thrombus in the capillaries of the stomach mucosa, leading to a slowing of blood flow, which leads to the development of ulcerations in the gastric mucosa (Fehri and Aiach, 2010). Therefore, the presence of flavonoids and polyphenols in the aqueous extract of *F. vulgare* may be associated with the anti-ulcer activity of this plant.

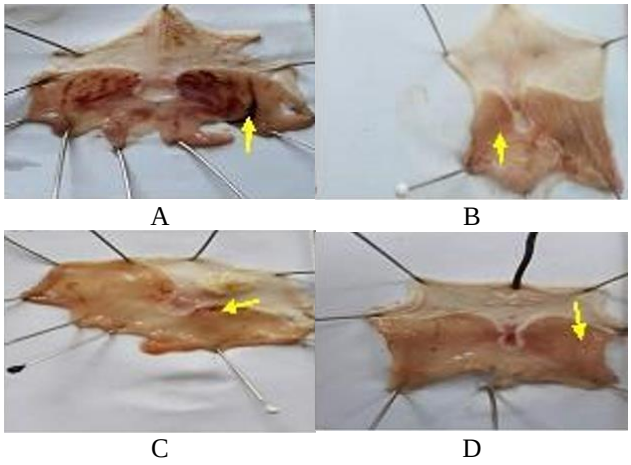

Figure 1. Effect of the aqueous extract of *F. vulgare* seeds on gastric ulcer induced by 70% ethanol.
A) Stomach of a mouse from the negative control group. B) Stomach of a mouse from the positive control group (ranitidine 5 mg/kg). C) Stomach of a mouse from the group treated with the 200 mg/kg extract. D) Stomach of a mouse from the group treated with the 400 mg/kg extract. (The arrows indicate the lesions).

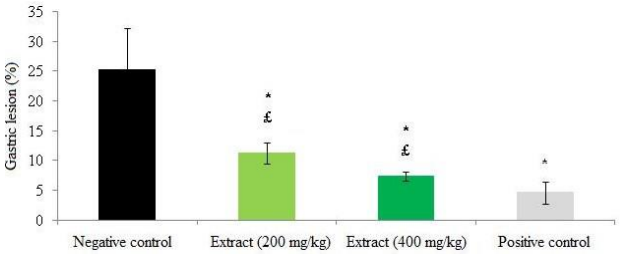

Figure 2. Effect of oral administration of *F. vulgare* extract (200 and 400 mg/kg) and ranitidine (5 mg/kg) on ulcer induced by ethanol (70%) in mice. Values were the mean ± SEM. *: Comparison to negative control; $P \leq 0.05$. £: Comparison against the positive control (ranitidine); $P \leq 0.05$

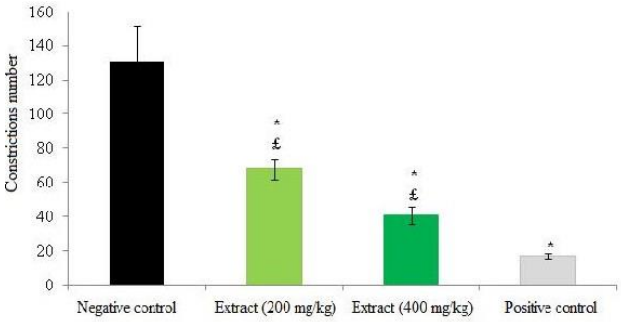

Figure 3. Analgesic effect of aqueous extract of *F. vulgare* (200 and 400 mg/kg) and Diclofenac (10 mg/kg) on abdominal constrictions induced in mice by injection of acetic acid. Values are mean ±SEM. *: Comparison with the negative control; P≤0.05. £: Comparison with the positive control (Diclofenac); P≤0.05.

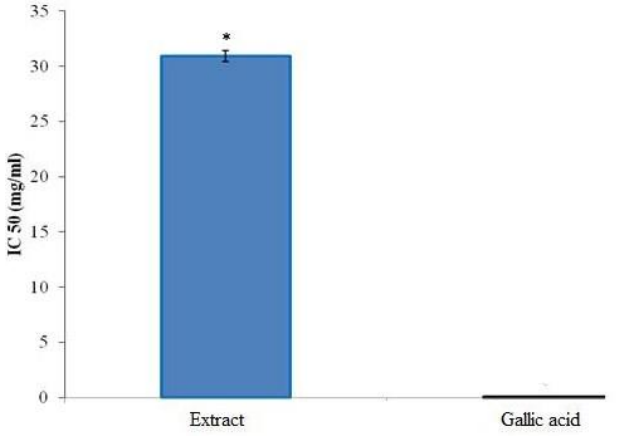

Figure 4. Comparison of IC_{50} value of aqueous extract of *F. vulgare* and gallic acid. Values are mean ± SEM (n=3). *: Comparison with gallic acid, P≤0.05

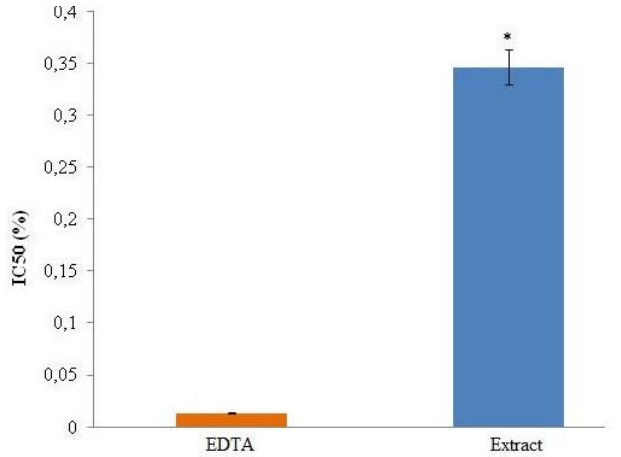

Figure 5. Comparison of the IC_{50} value of the aqueous extract of *F. vulgare* and EDTA. Values are mean ± SEM (n=3). *: Comparison with the EDTA; P≤0.05.

Analgesic activity

We performed a screening of the analgesic activity in the aqueous extract of the seeds of *F. vulgare*. The mechanism of onset of pain results from a tissue lesion responsible for an increase in the release of numerous chemical mediators such as: histamine, prostaglandin and serotonin, in the intraperitoneal fluid, which will stimulate the nociceptive receptors located at the peritoneal level. The effect was assessed by monitoring the number of abdominal constrictions induced by intraperitoneal injection of acetic acid (0.6%) in mice. The results showed that the intraperitoneally injection of acetic acid causes an average of 130.17±21.62 constrictions in the negative control group. In the presence of *F. vulgare* extract at 200 and 400 mg/kg, the number of constrictions decreases to 67.86±6.01 and 40.80±5.19 respectively (Figure 3), which corresponds to a percentage inhibition of 47.89% for the 200 mg/kg dose and 68.65% for the 400 mg/kg dose. While diclofenac reduced the number of constrictions up to 17±1.41 with an inhibition percentage of 86.93% compared to the negative control. Statistical analysis of the number of constrictions showed a significant difference between the negative control, the two doses of the extract and the positive control. At the same time, it revealed the absence of difference between the 400 mg/kg dose and diclofenac 10 mg/kg, which leads to the conclusion that the aqueous extract of *F. vulgare* 400 mg/kg had a significant analgesic activity. Our results are in agreement with those obtained by Monalisa and Rahmatullah (2015), who found a percentage inhibition of 40.7 and 44.7% at doses of 200 and 400 mg/kg respectively of the methanolic extract of the seeds of *F. vulgare*. While Choi and Hwang (2004) showed that the oral administration of the methanolic extract of this plant had an antinociceptive effect in the thermal nociception test and that this effect is due to components such as anethole and flavonoids. The study by Zendehdel et al. (2012) revealed that the aqueous extract of *F. vulgare* caused a significant reduction in nociception 48.4%, 62.7% and 70.7 at doses of 50, 100 and 200 mg/kg respectively. Acetic acid-induced pain may be due to increased production of prostaglandins and prostacyclins mediated by cyclooxygenases and lipooxygenases (Monalisa and Rahmatullah, 2015). *F. vulgare* extract had in its chemical composition polyphenols such as flavonoids which are inhibitors of cyclooxygenase, therefore the production of prostaglandin (Okwu and Josiah, 2006). Therefore, the analgesic effect of this extract may be partly due to the presence of these secondary metabolites.

Antioxidant activity

Antiradical test with DPPH

The antiradical activity of the aqueous extract of fennel seeds was evaluated by the DPPH method with comparison with gallic acid. The IC_{50} values were calculated, in order to determine the concentrations which reduce 50% of the free radicals. In the present study, the aqueous extract of *F. vulgare* seeds and gallic acid were able to reduce the DPPH radical with IC_{50} values of 30.91±0.49 mg/mL and 0.038±0.0002 mg/mL, respectively (Figure 4). These results showed that the extract of this plant had a less anti-radical activity than the reference antioxidant, gallic acid. Hilmi et al. (2014) showed that the ethanolic extract of *F. vulgare* fruits inhibits the free radical DPPH by 60.7±0.06%. On the other hand, an inhibition of 69.4±0.003% was observed with the aqueous extract of this plant. The antioxidant activity of the ethyl acetate extract of fennel seeds evaluated by the DPPH method also revealed a good antiradical capacity with an IC_{50} value of 1.5 µg/mL (El Quariachi et al., 2014). While Anwar et al. (2009) found an IC_{50} value of 1.5 µg/mL for the ethyl acetate extract and 6.2 µg/mL for the diethyl ether extract

from the same plant. This difference may be partially due to the studied part of the plant and to the extraction solvent. Statistical analysis showed that there is a significant difference between the IC_{50} value of the extract and that of the standard ($P \leq 0.05$). Indeed, the *F. vulgare* extract is characterized by a weaker antiradical capacity than that of the standard tested despite its richness in flavonoids. This may be due to the possible presence of glycosylated compounds (glycosylated flavonoids) characterized by their low biological activity.

Iron chelating power

To assess the chelating power of a given extract, the most commonly used stabilizing compound is ferrozine (Zhao et al., 2006). Indeed, ferrozine forms with the free iron present in a reaction medium, a ferrozine-Fe^{2+} complex of intense violet color. The quantification of this complex by spectrophotometry at 562 nm in a medium of known iron concentration provides information on the ability of the extract to chelate this element. The results obtained after studying the chelating activity of the aqueous extract of fennel seeds showed an IC_{50} values of 0.346±0.003 mg/mL and 0.013±0.006 mg/mL for the extract and the EDTA respectively (Figure 5). The statistical analysis revealed an iron chelation activity of the extract lower than that of EDTA. Despite this, the results obtained are good for a natural product. Indeed, Bettaieb Rebey et al. (2016) evaluated the antioxidant activity of different extracts of the seeds of *F. vulgare*, and they found that the ethanolic extract of Tunisian and Indian plants have a high ferrous ion chelating power and present an IC_{50} values of around 1.11 and 2.17 mg/mL. Likewise, Hilmi et al. (2014) showed that the ethanolic extract of *F. vulgare* fruits has a weak chelating activity (3.6±0.05%) and they find no chelating power for the aqueous extract of the same plant. Polyphenols are metal chelators and can inhibit Fenton and Haber-Weiss reactions, which generate hydroxyl radicals (Kanatt et al., 2010). Flavonoids possess greater antioxidant capacity against peroxidation induced by metal ions than that induced by peroxyl radicals (Rodrigo et al., 2011). Based on these results and because of the high content of polyphenols and flavonoids in the extract studied, we can say that the strong chelating power of *F. vulgare* may be due to the presence of these compounds.

Conclusion

In traditional medicine of Algeria, several natural products have been used to treat gastric ulcer and pain. *F. vulgare* is a medicinal plant popularly used in Algeria as anti-obesity, anti-anxiety, and galactagogue agent and for the treatment of gastrointestinal disorders. In this study, antiulcer, analgesic and antioxidant activities of the aqueous extract of *F. vulgare* seeds were studied. The extraction of bioactive compounds from this plant by decoction gave a considerable content of phenolic compounds. The evaluation of the analgesic effect of the aqueous extract of *F. vulgare* by counting abdominal constrictions induced by acetic acid as an algogenic agent showed that the extract has an important inhibition of pain. In a model of gastric ulcer induced by ethanol in mice, the extract gave a good gastro-protective effect with a percentage of protection which reaches 71% with a dose of 400 mg/kg. Fennel seed extract had considerable antioxidant activity, which has been evaluated, *in vitro*, by two tests: a DPPH radical scavenging power with an IC_{50} value of 30.91 mg/mL and an iron chelating activity, although it is weak in comparison to that of EDTA, but it can be considered high for a natural product.

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