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Research Article

Protective effects of total flavonoids from *Alpinia officinarum* rhizoma against ethanol-induced gastric ulcer *in vivo* and *in vitro*

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Context

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Objecti

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Materia

In vivo: Gastric damage was induced in BALB/c mice by administering ethanol (10 mL/kg) after oral treatment with F-AOH at 126.8, 63.4 and 31.7 mg/kg or ranitidine (Ran) at 100 mg/kg (1 week of continuous gavage). In vitro: Gastric mucosal epithelial cells (GES-1) were incubated with F-AOH (8, 4 and 2 μg/mL) for 16 h and treated with 7% ethanol for 4 h. The extent of gastric damage was assessed histopathologically, and the expression of NF-κB, COX-2, TNF-α, iNOS and IL-1β was quantified by Western blot analysis. In addition, proinflammatory mediators and concentrations of motilin (MTL) and gastrin (GAS) were measured by ELISA test.

Results

F-AOH effectively reduced the ulcer index (from 23.4 ± 4.28 to 8.32 ± 1.5) and reduced release of inflammatory mediators (IL-1β, IL-6, TNF-α and PGE2), increased the content of nitric oxide and improved GAS and MTL secretion. The 50% inhibitory concentration (IC_{50}) of F-AOH on cell damage was 17 μg/mL. F-AOH increased ethanol-induced cell survival (from 47 to 85%) and inhibited the expression of NF-κB, COX-2, TNF-α, IL-1β and iNOS proteins.

Conclusions

F-AOH inhibits ethanol-induced gastric mucosal damage, provides a theoretical basis for galanga ion of galanga

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haemorrhagic damage to the gastric mucosal lesions and mucosal oedema (Park et al. 2008), inflammatory cell infiltration (Xie et al. 2017) and diffuse ulcers (Al-Sayed and El-Naga 2015). NF-κB is one of the important transcription factors regulating the development of gastric ulcer. Its activation can regulate the immune response and the release and expression of proinflammatory mediators such as TNF-α, IL-1β, IL-6 and COX-2, thus aggravating ulcer injury (Chang et al. 2015; Chen et al. 2019). In ethanol-induced gastric ulcer, PGE2 was found to be associated with promoting the regeneration of gastric mucosal epithelial cells, repairing the ulcerous area and inhibiting gastric acid secretion. NO promotes the healing of gastric ulcer by improving mucosal microcirculation and scavenging oxygen free radicals (Elliott and Wallace 1998; Takeuchi et al. 2001; Yu et al. 2015). Moreover, ethanol exacerbates the extent of gastric ulcer by enhancing gastric contraction and small bowel movements, promoting gastric emptying and the pathogenesis of gastric acid secretion (Konturek et al. 1994).

Alpinia officinarum Hance (Zingiberaceae) is widely distributed in many tropical regions of Asia. In China, it is mainly distributed in Guangdong, Hainan and Yunnan. Its main chemical components are volatile oil, flavonoids and diarylheptanoids, which were found to treat digestive diseases such as indigestion, acid reflux and gastric ulcer. Many studies demonstrated its pharmacological activities, such as antibacterial (Zhang et al. 2010), antioxidant, (Ly et al. 2003), antitumor (Tabata et al. 2009) and anti-

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Plant material

Rhizomes of A. officinarum were collected from Haikou County, Hainan Province, China, in October 2017. The plant was identified by Professor Niankai Zeng of Hainan Medical University. A voucher specimen of this collection (no. 20171024) has been deposited in the Laboratory of Natural Pharmaceutical Chemistry of Hainan Medical University. The plant materials were air-dried and weighed, which were then grounded into coarse powder by a grinder (XL-06A, Xu Machinery, Guangzhou, China).

Preparation of plant extract

An aliquot (1 kg) of fresh Alpinia officinarum rhizomes was weighed precisely and refluxed with eightfold 80% ethanol for 1 h. The residue was extracted twice under the same conditions. The sampled ethanol extracts were combined and concentrated to 40% under reduced pressure. Then, the extract was purified with AB-8 macroporous resin by 80% ethanol. The ethanol elution fraction was subjected to silica gel column chromatography and eluted with a petroleum ether-ethyl acetate gradient to obtain six crude components (1–6), with components 4 and 5 being subjected to gel column chromatography and eluted with methanol.

Phytochemical analysis

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Animals

A total of 60 BALB/c female mice (18–22 g) from Tianqin Biotechnology (Changsha, China) were housed under controlled conditions (12 h light/dark cycle and room temperature of 24 ± 1 °C and 40–60% relative humidity). They had free access to food and water. All animal experiments were carried out in accordance with the recommendations of the International Guidelines for the Use and Care of Experimental Animals and conducted with the permission from the Animal Experimental Ethics Committee of Hainan Medical University (no. hy2018031601, Haikou, China).

Cell culture

Human gastric mucosal epithelial cells (GES-1) (Procell Life Science & Technology, Wuhan, China) were cultured at 37 °C under 5% CO_2 in RPMI 1640 culture medium (Gibco, Brooklyn, NY) supplied with 10% heat-inactivated foetal bovine serum (FBS) (Biological Industries, Beit Haemek, Israel), 100 U/mL of penicillin and 100 μ/mL of streptomycin (Beyotime, Nanjing, China).

Animal experiment design

After three days of adaptive feeding, the mice were randomly divided into six groups: normal group, ranitidine control group (100 mg/kg), ethanol group and F-AOH high-
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GES-1 cells were seeded on a 96-well plate at a density of 1×10^4 cells per well for 4 h and then treated with F-AOH (16, 8, 4, 2 and 1 μg/mL), while the normal group and the ethanol group were cultured in a serum-free medium, followed by incubation at 37 °C for 16 h. The normal group was stimulated with an equal volume of serum-free medium, while 7% alcohol was added and co-incubated for 4 h; 10 μL cell counting kit-8 (CCK-8) and 90 μL serum-free medium were added into each well. After incubation for 2 h in a cell culture incubator, the optical density (OD) value was then measured on a microplate reader at 450 nm. The cell viability was calculated according to the equation:

$$\text{Cell viability} = [(As-Ab)/(Ac-Ab)]\times 100\% \quad (1)$$

where As is the OD of the F-AOH group or OD of the ethanol group, Ab is the OD of the blank hole and Ac is the OD of the normal group.

Determination of the injury index of gastric ulcer

The ulcer index (UI) was calculated according to the following equation:

$$\text{Ulcer index (UI)} = (1A)+(2B)+(3C) \quad (2)$$

where A is the number of small ulcers ≤1 mm, B: 3 mm ≥ the number of ulcer >1 mm and

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The levels of proinflammatory cytokines TNF-α, IL-1β and IL-6 in gastric tissue and GES-1 supernatant were determined using an ELISA kit (Elisa Biotech, Shanghai, China). Simultaneously, the levels of PGE2, NO, motilin (MTL) and gastrin (GAS) and the activities of iNOS and COX-2 were also measured. The OD value was then measured on a microplate reader at 450 nm (BioTek Instruments, Inc., Winooski, VT). All tests were performed according to the manufacturer's recommendation.

Western blot analysis

Homogenized gastric tissue was lysed with radioimmunoprecipitation assay (RIPA) lysis buffer (Beyotime, Nanjing, China) containing protease and phosphatase inhibitors. Then, the solution was centrifuged at 12,000×g at 4 °C for 5 min. The supernatant was collected and concentrations were then determined using bicinchoninic acid (BCA) protein assay kit (Beyotime, Nanjing, China). Equal amounts of protein samples were separated by 8% sodium dodecyl sulphate-polyacrylamide gel electrophoresis (SDS-PAGE) and transferred onto polyvinylidene fluoride (PVDF) (MilliporeSigma, Burlington, MA) membranes. The PVDF membranes were blocked with 5% BSA for 1 h on a shaker, then incubated with 1:1000 dilution of primary anti-NF-κBp65 (Abcam, cat. no. Ab16502), COX-2 (Abcam, cat. no. ab15191), TNF-α (Abcam, cat. no. ab9739), iNOS (Abcam, cat. no. ab15323), IL-1β (Abcam, cat. no. Ab2105) and β-actin (Abcam, cat. no. Ab8245) at 4 °C overnight, and subsequently processed on a shaker at room tempera l antibody. Finally, t cules, CA) using ch Densitor l Institutes of Healt

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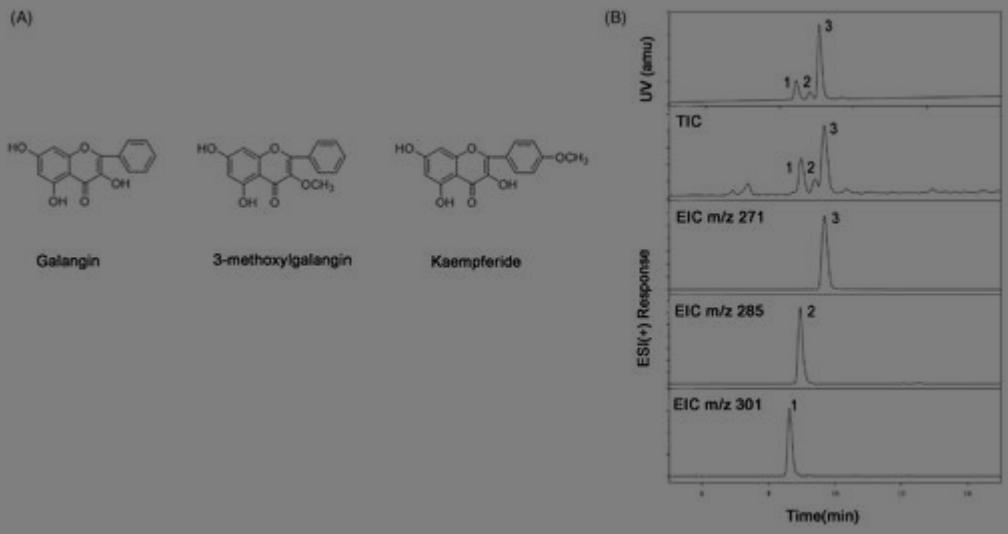
Result

Identification of F-AOH components

Figure 1(A) presents the primary active ingredients of F-AOH. It was found that the flavonoids contained galangin (1), 3-methylgalangin (2) and kaempferide (3) (Figure 1(B)).

Figure 1. Chemical structures of the three major constituents in the flavonoid fraction. (A) Galangin: 3, 5, 7-trihydroxyflavone; 3-methyl Galangin: 5, 7-Dihydroxy-3-methoxyflavone; Kaempferide: 3, 5, 7-trihydroxy-4-methoxyfla-vone. (B) UHPLC-DAD-MS of F-AOH (1. Kaempferide; 2. 3-methyl Galangin; 3. Galangin).



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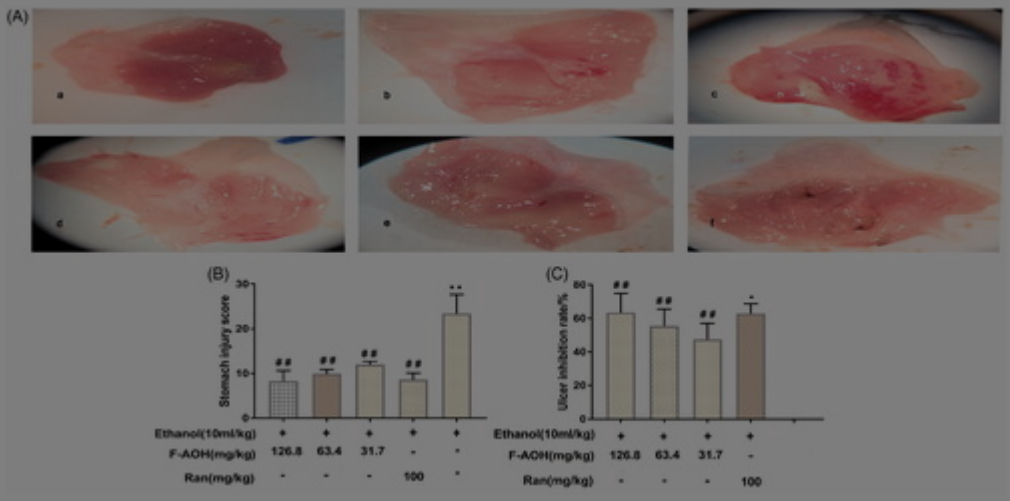
group. Values are expressed as means ± standard deviation (n = 8). *p < 0.05, compared with normal group; #p < 0.05 and ##p < 0.01, compared with ethanol group. (C) Percentage of treatments group inhibition. *p < 0.05 compared with Ran group; ##p < 0.01 compared with ethanol group.



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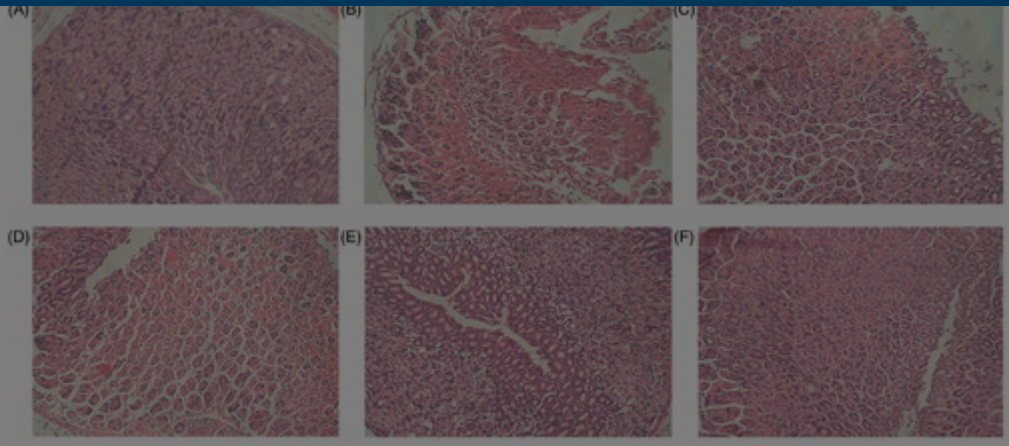
Histopathological examination

The histopathological evaluation of gastric tissues (Figure 3) shows that the normal group did not undergo any significant histopathological changes, demonstrating complete tissue structure; neatly arranged somatic cells; and no gastric mucosal erosion, cell infiltrati ty of the gastric t e ulceration and eros anged and damage Compared with the) or Ran (100 mg ory cell infiltrati

Figur H&E staining); (D) F-AOH (31.7 mg



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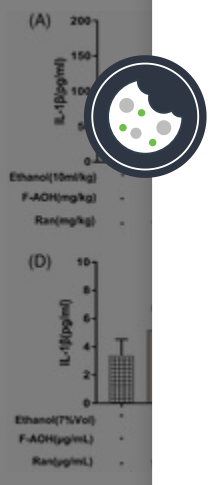
Determination of proinflammatory factors

Ethanol treatment in mice resulted in a significant increase in the levels of TNF-α, IL-1β and IL-6 as compared with those of the normal group ($p < 0.01$, Figure 4). In the meantime, treatment with F-AOH lowered the elevated levels of proinflammatory cytokines in gastric tissue ($p < 0.01$, Figure 4(A–C)) and in the cell supernatant (Figure 4(D–F)). F-AOH treatment at 63.4 mg/kg significantly reduced the expression of IL-1β, IL-6 and TNF-α when compared with Ran treatment (100 mg/kg) and F-AOH treatment at 126.8 and 31.7 mg/kg. In cell experiments, the inhibition of proinflammatory factor levels was optimally suppressed by F-AOH (4 μg/mL) ($p < 0.01$, Figure 4(D–F)). Compared with ethanol treatment, in vitro/in vivo experiments demonst F TNF-α, IL-1β and I

Figure 4 cells (D–F). Values a **$p < 0.01$ compare anol group.



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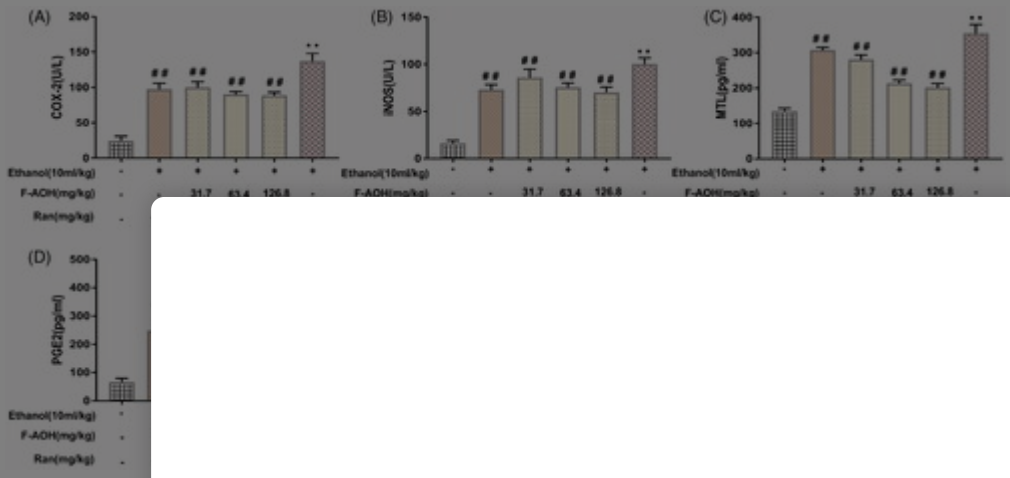
Effect of F-AOH on the levels of MTL, GAS, PGE2 and NO and on the activities of iNOS and COX-2

Compared with the normal tissues, the levels of PGE2, MTL, GAS and NO and the activity of COX-2 and iNOS in ethanol-induced gastric tissues were significantly increased ($p < 0.01$, Figure 5). Treatment with F-AOH and Ran could lower the elevated activities of COX-2 and levels of PGE2 ($p < 0.01$, Figure 5(A,D)). F-AOH (63.4 and 126.8 mg/kg) significantly inhibited the production of MTL, when compared with Ran (100 mg/kg) and F-AOH treatment (31.7 mg/kg) ($p < 0.01$, Figure 5(C)). Treatment with F-AOH also inhibited the increase in GAS ($p < 0.01$, Figure 5(F)). In addition, F-AOH can also increase NO content and reduce iNOS activity ($p < 0.05$, Figure 5(B,E)).

Figure 5. Effect of F-AOH on the levels of PGE2, MTL, GAS, NO and on the activities of iNOS and COX-2 (A–B) Effects of F-AOH on the activities of iNOS and COX-2. (C–F) Effects of F-AOH on the Levels of PGE2, NO, MTL, and GAS. Values are expressed as means ± standard deviation ($n = 6$). **$p < 0.01$ compared with normal group; #$p < 0.05$ and ##$p < 0.01$ compared with ethanol group.



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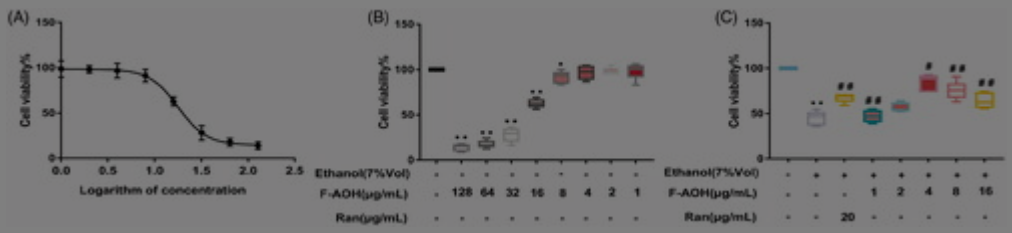
and then decreased with the increase of F-AOH concentration. When the concentration of F-AOH was controlled at 4 μg/mL, the cell activity was optimal. Interestingly, when the concentration of F-AOH is greater than that in the F-AOH group treated with 4 μg/mL, the cell activity decreases as the drug concentration increases. We believe that this may be related to the inhibition of cell activity by excessive drug concentration. Considering the dose factor and concentration limits, we selected the F-AOH groups treated with 8, 4 and 2 μg/mL as the drug group. The results showed that the active ingredient in F-AOH is effective against ethanol-induced gastric mucosal cell damage.

Figure 6. Defensive effects of F-AOH. (A) IC50 of F-AOH on the viability of GES-1 cells was examined. (B) Various concentrations of F-AOH (0, 1, 2, 8, and 16 μg/mL) were used to detect their effects on cell viability. (C) Various concentrations of F-AOH were used to attenuate ethanol-induced inhibition of cell viability. Values are expressed as means ± standard deviation ($n = 6$). *$p < 0.05$ compared with normal group; #$p < 0.05$ and ##$p < 0.01$ compared with ethanol group.



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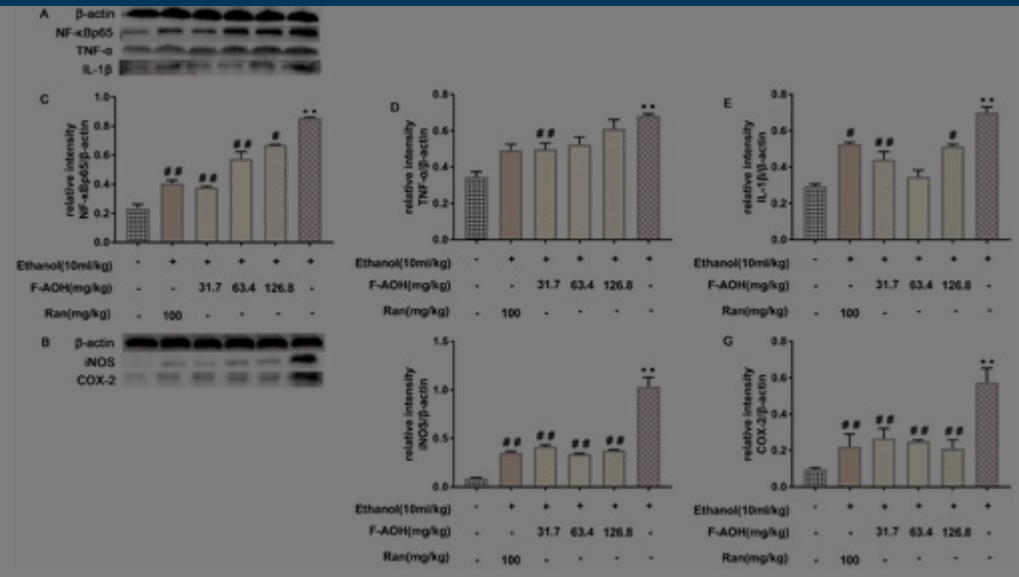

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Discussion

The ethanol-induced gastric ulcer model has been widely used in the treatment of gastric ulcer and in the study of protective mechanisms of drugs. Subsequently, the mouse model of acute gastric ulcer was established in accordance with the ethanol-induced method to explore the effects of F-AOH on acute gastric ulcer. In addition, some previous studies reported that the extract of A. officinarum has anti-inflammatory activity (vides us with the stimulation is associ in gastric tissue, c death of epithelia), and tissue degener stent with our expe ces these chan nol-induced gastri stric mucosal damage

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2018) and inducing the activation of the NF-κB signalling pathway (Rozza et al. 2014). Studies have shown that the release and expression of IL-1β and IL-6 play an important role in gastrointestinal diseases such as gastric ulcer (Plebani et al. 1995), gastric cancer (Kabir et al. 1995) and colitis (Yamamoto et al. 2000; Wang et al. 2014). They could participate in the inflammatory process by upregulating the expression of endothelial cell adhesion molecules in tissues and serum and by inducing lymphocyte activation and differentiation, including the aggregation, activation and infiltration of inflammatory cells. Therefore, IL-1β and IL-6 levels can be used as indicators to evaluate the severity of ethanol-induced acute gastric ulcer, and so inhibiting the release of inflammatory cytokines is considered as one of the effective methods of reducing the severity of gastric mucosal injury. In our experiment, the levels of proinflammatory cytokines in gastric ulcer tissue and GES-1 cell supernatant were significantly increased in the ethanol-induced model. We found that the mucosa of gastric ulcer tissue was damaged; epithelial cells were decreased, destroyed or randomly arranged; and ulceration and erosion were formed in the tissue as confirmed by direct visualization and histopathological methods. However, the levels of TNF-α, IL-1β and IL-6 in tissue and GES-1 cell supernatant were significantly decreased, and the corresponding gastric ulcer and mucosal integrity were improved in the Ran and F-AOH groups. This finding demonstrates that F-AOH inhibits ethanol-induced gastric mucosal damage and local ulceration by inhibiting the production of proinflammatory factors.

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1997). Ethanol can induce NO release through iNOS overexpression and react with superoxide anion (O_2^-) to form peroxynitrite ($ONOO^-$), which leads to lipid peroxidation damage of gastric tissue and accelerates gastric mucosal damage (Al-Quraishy et al. 2017). This is in agreement with that of our experimental results: the expression of NO in ethanol-induced gastric ulcer tissue is significantly increased. Interestingly, we found that F-AOH did not reduce the expression of NO, but continued to increase the level of NO. We believe that the underlying mechanism of F-AOH to promote the healing of gastric ulcers is to further increase the NO content on the basis of stimulating ethanol-induced iNOS production in the short term, thereby quickly completing the inflammatory response and contraction of ulcers, improving mucosal microcirculation, and effectively removing oxygen free (Elliott and Wallace 1998). In addition, in the early stage of physiologic inflammation, a low concentration of NO can activate the NF-κB pathway through its own amplification and the interaction of proinflammatory factors. When the concentration of NO increases abnormally, it can generate negative feedback to the NF-κB pathway and block its activation. At the same time, it can also lead to the suppression of the transcription of target genes related to NF-κB, including iNOS that promotes the increase of NO in the early stage, which in turn reduces NO and other inflammatory factors and accelerates the completion of the inflammatory response (Park et al. 1997). In our experiment on detecting iNOS activity and protein expression, we found that, compared with the model group, the iNOS activity and protein expressi oduced in the early OS and inhibit th considered as one o n the ethanol-

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As generally known, gastric acid is one of the key factors that play an important role in the development of gastric ulcer (Wijeratne et al. 2015). GAS can promote the synthesis of gastric acid and pepsin, stimulate the vagus nerve, and enhance the physiological function of gastric motility. MTL can promote gastric motility, smooth muscle contraction and gastric emptying. In our study, GAS and MTL levels increased significantly in the ethanol group, indicating that ethanol-induced ulcer could block the physiological feedback of GAS and MTL in the stomach and aggravate the degree of gastric mucosal injury through the increase of both levels in gastric tissues. However, the levels of GAS and MTL decreased significantly in gastric tissues after pre-treatment with F-AOH and Ran, suggesting that F-AOH can affect the secretion of GAS and MTL, thereby improving gastric acid and gastrointestinal motility and promoting ulcer healing.

Conclusions

The results showed that F-AOH had anti-inflammatory and protective effects on ethanol-induced gastric ulcer. The underlying mechanism may be related to the abnormally increased negative feedback regulation of NO, the activation of NF-κB/COX-2 signalling pathway, and the influence of downstream inflammatory factor levels. These fi n the Chinese vity and anti-infla rotective agent. F ects of F-AOH on echanism of the fe COX-2 and downstr

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Funding

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