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Anti-ulcerogenic effect of cavidine against ethanol-induced acute gastric ulcer in mice and possible underlying mechanism

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ABSTRACT

Cavidine, a major alkaloid compound isolated from *Corydalis impatiens*, has various pharmacological effects but its effect on gastric ulcer has not been previously explored. The current study aimed to investigate the possible anti-ulcerogenic potential of cavidine in the model of ethanol-induced gastric ulcer. Mice received cavidine (1, 5 or 10 mg/kg, ig), cimetidine (CMD, 100 mg/kg, ig) or vehicle at 12 h and 1 h before absolute ethanol administration (0.5 mL/100 g), and animals were euthanized 3 h after ethanol ingestion. Gross and histological gastric lesions, biochemical, immunological and Western blot parameters were taken into consideration. The results showed that ethanol administration produced apparent mucosal injuries with morphological and histological damage, whereas cavidine pre-treatment reduced the gastric injuries. Cavidine pre-treatment also ameliorated the contents of malonaldehyde (MDA) and myeloperoxidase (MPO) activity, and increased the mucosa levels of glutathione (GSH), superoxide dismutase (SOD) and prostaglandin E_2 (PGE_2), relative to the model group. Also cavidine was able to decrease the levels of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), inhibit the up-regulation of cyclo-oxygenase-2 (COX-2) expression and activation of Nuclear factor-kappa B (NF-κB) pathway. Taken together, these results indicated that cavidine exerts a gastroprotective effect against gastric ulceration, and the underlying mechanism might be associated with the stimulation of PGE_2, reduction of oxidative stress, suppression of NF-κB expression and subsequent reduced COX-2 and pro-inflammatory cytokines.

1. Introduction

Peptic ulcer disease, also known as a peptic ulcer or stomach ulcer, is the most common multifactor gastrointestinal disorder affecting millions of people worldwide. Signs and symptoms of peptic ulcer can include one or more of the followings: abdominal pain, bloating, poor appetite, weight loss, nausea or vomiting. Although the exact pathophysiology of gastric ulcer is unknown, the delicate balance between some defensive and aggressive factors result in peptic ulcer [1–3]. The incidence of gastric ulcer is increased due to over ingestion of non-steroidal anti-inflammatory drugs (NSAID), *Helicobacter pylori*, stress, smoking, and alcohol. Among the various factors, alcohol consumption is the greatest contributor to gastric injury [4]. It is well known that alcohol is one of the most commonly abused drugs, and related to a variety of physical, mental as well as social damage. Consumption of excessive alcohol generally weakens gastric mucosal defense and induces gastric mucosal injuries including gastritis and ulcer, which may progress to gastric cancer [5]. Thus, the experimental model of gastric ulcer is often induced by ethanol. Using such animal models, researchers simulate conditions to which humans may be exposed and, as a result, develop gastric ulcer [6].

Previous studies reported that oxidative stress and inflammation were greatly responsible for gastric injury. Oxidative stress, which is a state of unbalanced levels of reactive oxygen species (ROS), can cause gastric mucosal injuries including ulceration, erosion and hemorrhage. Oxygen derived free radicals, primarily hydroxyl radicals, super-oxide anions, and lipid peroxides, are the harmful species known to cause the gastric ulcer [7,8]. A major source of ROS in ethanol-injured gastric tissue is the infiltration of activated neutrophils. The neutrophils infiltration into the gastric mucosal tissues is evaluated by the activity of myeloperoxidase (MPO) [9,10]. The activated neutrophils will stimulate the release of several pro-oxidative enzymes and free radicals, which lead to oxidative burst [11,12]. Gastric cell have several antioxidant enzymes such as superoxide dismutase (SOD) and glutathione (GSH) to scavenge ROS, but sustained generation of ROS enhance lipid peroxidation and deplete these antioxidants enzymes. Therefore, it is significant to maintain balance between reactive oxygen metabolites and antioxidant defense systems in the process of protecting gastric mucosal from ethanol-induced oxidative damage. Many studies have confirmed that pro-inflammatory cytokines such as tumor necrosis factor-alpha

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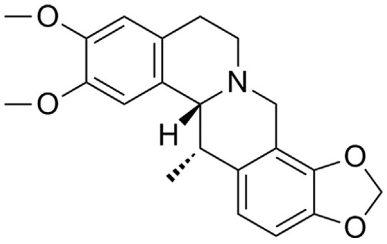

Fig. 1. Chemical structure of cavidine.

(TNF-α) and interleukin-6 (IL-6) are key mediators in the pathophysiology of gastric inflammation [13–15]. TNF-α, as the most prominent "first-line" cytokine, can induce the production of reactive oxygen species and oxidative stress-responsive genes to amplify and prolong inflammatory injury [16]. IL-6, as a pleiotropic cytokine, can activate neutrophils, lymphocytes and macrophages at the inflammatory site, which in turn initiate different oxidative bursts and toxic metabolites responsible for local tissue damage [17,18]. NF-κB is the classic pro-inflammatory transcription factor containing p50/p65 and IκB, and controls the transcription of inflammatory cytokines. Many stimulus can lead to the activation of NF-κB through the phosphorylation of inhibitors of κB (IκBs) by the IκB kinase (IKK) complex. Subsequently, the freed NF-κB translocate into the nucleus and triggers the transcriptional activation of several pro-inflammatory mediators [19]. Because NF-κB plays a critical role in the process of inflammatory response, suppression of NF-κB pathway may be a target for the treatment of gastric ulcer.

Prostaglandins (PGs) mediates pain and supports the inflammatory process. The biosynthesis of PGs in the gastrointestinal tract is exclusively catalyzed by the cyclooxygenase-1 (COX-1), besides of the data verifying the role of the inducible form COX-2, as well [20]. Prostaglandin E_2 (PGE_2), which play an essential role in the maintenance of gastric mucosal integrity, can be decreased by ethanol [21,22]. Thereby, the restoration of PGE_2 levels to normal value can alleviate ethanol-induced gastric mucosa injury.

Corydalis impatiens has been widely used for treatment of skin injuries, hepatitis, cholecystitis and scabies as a traditional Tibetan herb for centuries. Cavidine (see Fig. 1), an isoquinoline alkaloid from *C. impatiens*, has a variety of biological and pharmacological activities such as anti-inflammatory, anti-tumor, anti-bacterial [23]. Previously, we have

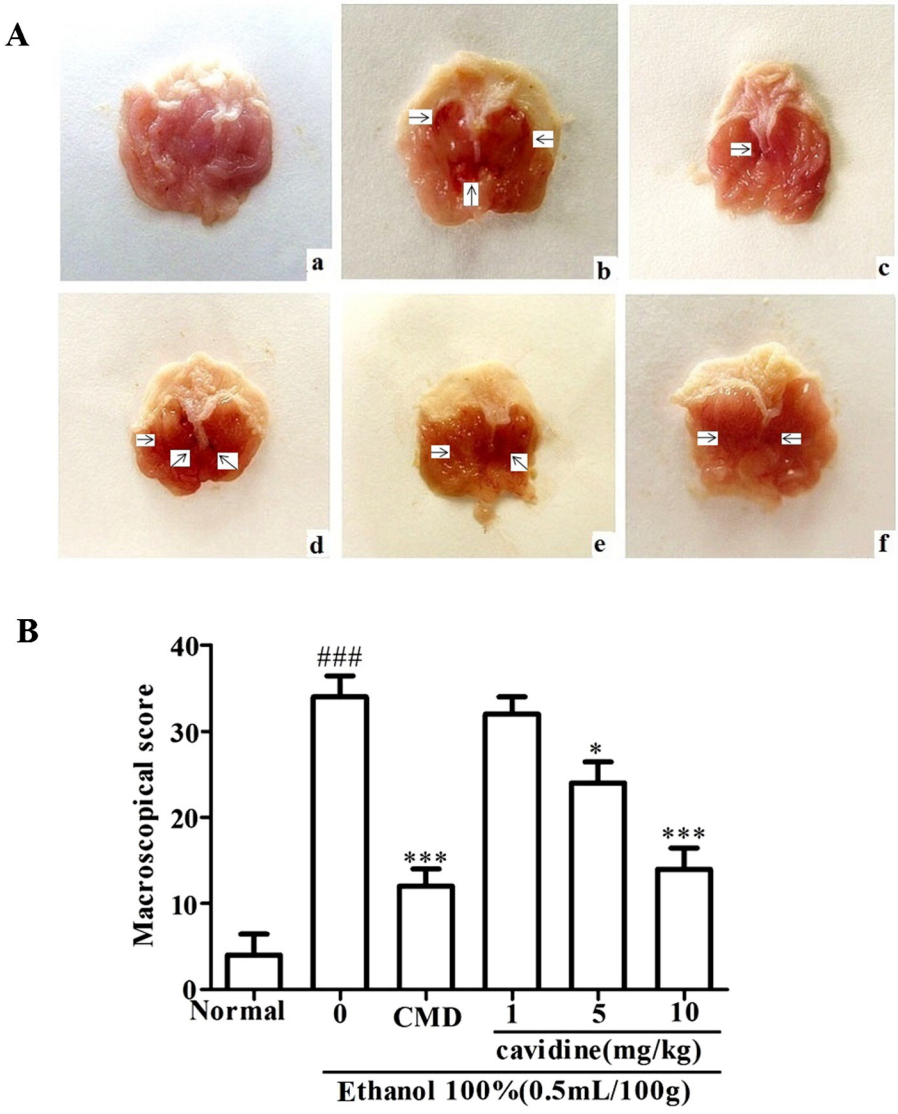

Fig. 2. Effects of cavidine on the macroscopic morphology of the gastric mucosa in ethanol-treated mice. (A) Macroscopic appearances of the gastric mucosa of mice challenged with ethanol. (a) Normal group; (b) ulcer control group; (c) CMD (100 mg/kg) group; (d) cavidine (1 mg/kg) group; (e) cavidine (5 mg/kg) group and (f) cavidine (10 mg/kg) group. The arrow showed severe hemorrhagic lesions in gastric mucosa induced by absolute ethanol. (B) Macroscopic evaluation of the gastric mucosa of mice challenged with ethanol. Data are expressed as the means ± S.E.M. $^{###}p < 0.001$, compared to the normal group; $^{*}p < 0.05$ and $^{***}p < 0.001$, compared to the ulcer control group.