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Original Research Article

Protective effect of evodiamine on acetic acid-induced gastric ulcers in rats through regulation of ROS/ICAM-1/Nrf2 signaling pathway

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Abstract

Purpose: *To study the effect of evodiamine on the signaling pathway of ROS/ICAM-1/Nrf2 in rats with acetic acid-induced stomach ulcers.*

Methods: *The rats were randomly assigned to five groups containing 10 rats each. Prior to acetic acid-induction of gastric ulcers, omeprazole (4.0 mg/kg/day), low-dose evodiamine (L-EVD, 20 mg/kg/day), and high-dose evodiamine (H-EVD, 40 mg/kg/day) were orally administered to the respective groups for 15 days. Following ulcer induction, the same treatments continued for an additional 7 days, for a total treatment duration of 22 days. The control (0.9 % saline) and acetic acid (model) groups were administered 0.9 % sodium chloride solution (10 mL/kg) for the same period. Thereafter, oxidative stress, inflammatory markers, macroscopic and microscopic evaluations were conducted on the gastric mucosa.*

Results: *The acetic acid group showed significantly higher levels of oxidative and inflammatory markers, as well as damage and degeneration of the gastric mucosa when compared to control group ($p < 0.05$). However, both low-dose and high-dose evodiamine treatment groups demonstrated significant gastric healing. Administration of low-dose and high-dose evodiamine resulted in significantly lower levels of malondialdehyde (MDA), tumor necrosis factor α (TNF-α), interleukin-1β (IL-1β), myeloperoxidase (MPO) and intracellular adhesion molecule-1 (ICAM-1, $p < 0.05$). Furthermore, evodiamine treatment led to significantly increased levels of glutathione (GSH) and nuclear fact-erythroid factor 2 (Nrf2).*

Conclusion: *Evodiamine reduces oxidative stress, suppresses inflammatory reactions, and exerts an anti-ulcer effect on acetic acid-induced gastric ulcers in rats by modulating ROS/ICAM-1/Nrf2 signaling pathway. More studies into the integration of evodiamine into conventional pharmaceutical treatments for gastric ulcers should be conducted.*

Keywords: *Evodiamine, Acetic acid, Gastric ulcer, Anti-oxidant, Anti-inflammatory*

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INTRODUCTION

Gastric ulcer (GU) is a prevalent condition marked by recurring episodes of epigastric discomfort and is frequently detected in the gastric lining. Gastric ulcers may result in complications such as hemorrhage, narrowing, perforation and blockage of the pylorus. GU is

regarded as a premalignant lesion for gastric cancer and significantly contributes to intestinal-type cancer progression [1]. Primary factors contributing to GU include *Helicobacter pylori* infection, excessive gastric acid secretion and impaired gastric mucosal barrier function [2]. Pathogenesis of gastric ulcers is predominantly influenced by the breakdown of gastric acid and proteases. Acetic acid-induced ulcer models are frequently employed in investigations of the pharmacology and pathophysiology of gastric ulcers [3].

Critical assessment parameters for gastric ulcers include inflammatory cytokines, reactive oxygen species (ROS) and regional blood flow in gastric tissues [4]. Presently, the therapeutic choices for gastric ulcers include medications such as acid pump inhibitors, antagonists of H2 receptors and therapy targeting the eradication of *Helicobacter pylori* [5]. However, despite the favorable treatment outcomes they offer, these therapies are linked to unwanted drug responses, drug resistance and elevated rates of recurrence. Therefore, there is an urgent need for an ideal anti-ulcer drug. The investigation into botanical extracts and herbal remedies may provide choices that are safer, more efficient and less likely to induce side effects for managing gastric ulcers.

Evodiamine (EVD) is an organic compound extracted from the immature fruits of *Evodia rutaecarpa*, a medicinal plant historically utilized for alleviating pain and reducing nausea and fever. Evodiamine (EVD) hinders tumor growth and alleviates inflammation with significant antioxidant activity [6]. However, this study was aimed at investigating the potential anti-ulcer properties of evodiamine in rats with acetic acid-induced gastric ulcers and uncovering the underlying mechanisms, particularly focusing on the involvement of the ROS/ICAM-1/Nrf2 signaling pathway.

EXPERIMENTAL

Animal handling

Fifty male Wistar rats, weighing between 180 - 220 g, were obtained from Changchun Yisi Experimental Animals Technology Co., Ltd. (Changchun, China). The animals were made to acclimatize for 7 days under standard laboratory conditions (40 - 60 % relative humidity, temperature maintained at 20 - 25 °C and a 12-hour light/dark cycle). Throughout the experiment, the rats were given unrestricted access to food and water. The study was conducted in strict adherence to the approved protocol of the Animal Care and Use Review Committee of Affiliated Haikou Hospital of Xiangya Medical School, Central South University (approval no. HK-XY-021), and complied with the internationally accepted guide for the care and use of laboratory animals, published by the US National Institutes of Health [7].

Animal groups and model

The animals were assigned randomly into five treatment groups each consisting of 10 rats; a control, an acetic acid-induced group (model group), (0.3 mL/kg acetic acid (Zibo Luzhong Chemical Light Industry Co. Ltd, Zibo, China)), a positive drug group treated with omeprazole (St. Louis, MO, USA) (4.0 mg/kg/day), a low dose evodiamine (Shanghai Yuan Ye Bio-technology Co. Ltd, B21315, 20 mg, Shanghai, China) (20 mg/kg/day; L-EVD) and a high dose evodiamine group (40 mg/kg/day; H-EVD). Dosages were determined based on preliminary studies [8]. All rats underwent a 16-hour fasting period and were then anesthetized. Laparotomy was conducted and 0.3 mL acetic acid was injected into the submucosa at the junction of the gastric body and pyloric antrum, excluding the control group. Prior to ulcer induction, omeprazole (4.0 mg/kg/day), low-dose evodiamine (20 mg/kg/day), and high-dose evodiamine (40 mg/kg/day) were orally administered to the respective groups for 15 days. Following ulcer induction, the same treatments continued for an additional 7 days, making the total treatment duration 22 days. The control and acetic acid groups received 0.9 % sodium chloride solution (10 mL/kg) for the same period.

Sample preparation commenced 2 h after the final administration of treatments on day 22. Anesthesia was induced, and the stomach of the rats were dissected along the greater curvature to evaluate the number and severity of ulcers.

Sample preparation

After 2 h following administration of acetic acid, anesthesia was induced. Following the procedure outlined by Abdel-Aziz *et al* [9], the stomachs of the rats were dissected along the greater curvature to evaluate the number and severity of ulcers. The excised tissues were rinsed with chilled saline solution, gently dried and weighed. Subsequently, a 10 % homogenate was generated by using a polytron homogenizer at 40 °C in 0.05 M phosphate buffer with a pH of 7. The homogenate was centrifuged at 10,000 rpm for 20 min to eliminate cellular debris, intact cells, cell nuclei, red blood cells and

mitochondria. Subsequently, the resulting supernatant containing the cytosolic extract, was utilized to evaluate malondialdehyde (MDA) (K739-100, Abcam, Cambridge, MA, USA kit), reduced gluthatione (GSH) (K464-100, Abcam, Cambridge, MA, USA kit), Nrf2 (ab207223, Abcam, Cambridge, MA, USA kit), tumor necrosis factor α (TNF-α) (438204, Biolegend, San Diego, CA, USA kit), IL-1β (SEA563Ra, Abcam, Cambridge, MA, USA kit), myeloperoxidase (MPO) (K464-100, Abcam, Cambridge, MA, USA) and intracellular adhesion molecule 1 (ICAM-1) (abx155662, Abbexa, Cambridge, UK) following the instructions provided with the respective kits. The absorbance was obtained within the range of 450 to 630 nm using an ELISA plate reader (Stat-Fax 2200, Awareness Technologies, Cary, NC, USA).

Evaluation of parameters/indices

Determination of oxidative stress biomarkers

Malondialdehyde (MDA)

The level of malondialdehyde (MDA) was determined by treating the samples with thiobarbituric acid (TBA) in an acidic medium at 95 °C for 30 min. This reaction led to the formation of a colourful TBA-reactive complex. Optical density of the complex was measured at 532 nm using spectrophotometry.

Reduced glutathione (GSH)

The GSH content was determined using 5,5'-dithiobis (2-nitrobenzoic acid) assays. The interaction between GSH and the reagent generated a yellow product whose intensity correlates with GSH level. Optical density was recorded at 405 nm using a spectrophotometer.

Nrf2 transcription

The stomach homogenate was added to microplates coated with human Nrf2 antibody and incubated. After incubation, the plates were washed to remove any unbound components. Subsequently, a second antibody conjugated with horseradish peroxidase was added to the plate and incubated again. This allowed the antibody to bind to the Nrf2 protein. The plates were rinsed, and a substrate solution was introduced, leading to a color development reaction. Thereafter, a stop solution was added and the optical density at 450 nm was read using a microplate reader (Thermo Scientific Multiskan GO, Waltham, MA, USA).

Inflammatory biomarkers (TNF-α, IL-1β, ICAM-1 and MPO)

The gastric homogenate (100 µL) was transferred to pre-coated 96-well plates containing specific antibodies against the corresponding inflammatory biomarkers. Subsequently, the plates were left to undergo incubation at room temperature for 2 h. Thereafter, the diluted biotinylated antibody (100 µL) was introduced and incubated at 37 °C for 1 h. Following this, the affinity-purified streptavidin-HRP conjugate (100 µL) was added to the 96-well plate and incubated at 37 °C for 30 min, with intermittent washing steps. Development of the reaction was initiated by the addition of 100 µL of TMB colorimetric substrate, followed by a reaction time of 15 - 30 min under conditions protected from light. The reaction was stopped by adding 100 µL of sulfuric acid solution, after which the absorbance at 450 nm was measured using a spectrophotometer.

Histo-architectural evaluations

Gastric samples were immersed in 10 % buffered formalin for fixation, processed through dehydration and clearing, embedded in paraffin and sectioned into slices of 5 µm thickness. The sections were stained with hematoxylin and eosin (H & E) and examined using an optical microscope.

Statistical analysis

Statistical analyses were conducted using GraphPad Prism 6 software (GraphPad Software, La Jolla, CA, USA). The results were obtained from triplicate determinations are presented as mean ± standard deviation (SD). Group comparisons were carried out using t-test or one-way analysis of variance (ANOVA). $P < 0.05$ was considered statistically significant.

RESULTS

Evodiamine prevents acetic acid-induced gastric ulcers

Acetic acid-treated group showed significantly higher quantity and intensity of gastric ulcers compared to control group ($p < 0.05$). However, omeprazole and low and high-dose evodiamine exhibited significantly lower quantity and intensity of gastric ulcers compared to the acetic acid-treated group ($p < 0.05$, Figure 1 A and B).

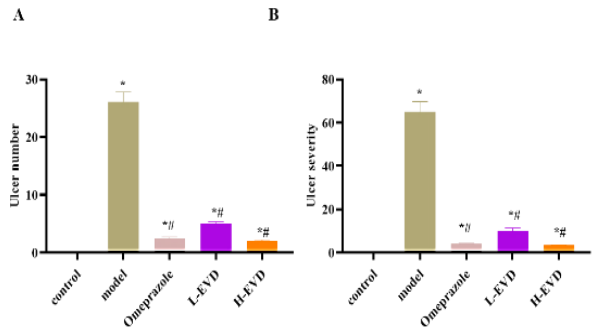

Figure 1: Evodiamine exhibits significant preventive effect on acetic acid-induced gastric ulcers. (A) Analysis of ulcer count; (B) Analysis of the degree of gastric ulcer severity. *P < 0.05 vs control group, $^{\#}p$ < 0.05 vs acetic acid treated group (model group)

Oxidative biomarkers (MDA, GSH and Nrf2)

Model group showed significantly higher MDA (Figure 2 A), and lower GSH (Figure 2 B) and Nrf2 (Figure 2 C) levels compared to control group (p < 0.05). In contrast, omeprazole, low-dose and high dose evodiamine groups exhibited significant decrease in MDA concentration compared to model group. Furthermore, concentrations of GSH and Nrf2 were significantly higher in omeprazole, low-dose, and high-dose evodiamine-treated groups compared to model group (p < 0.05). These findings indicate that evodiamine exhibits dose-dependent gastroprotective effects (Figure 2).

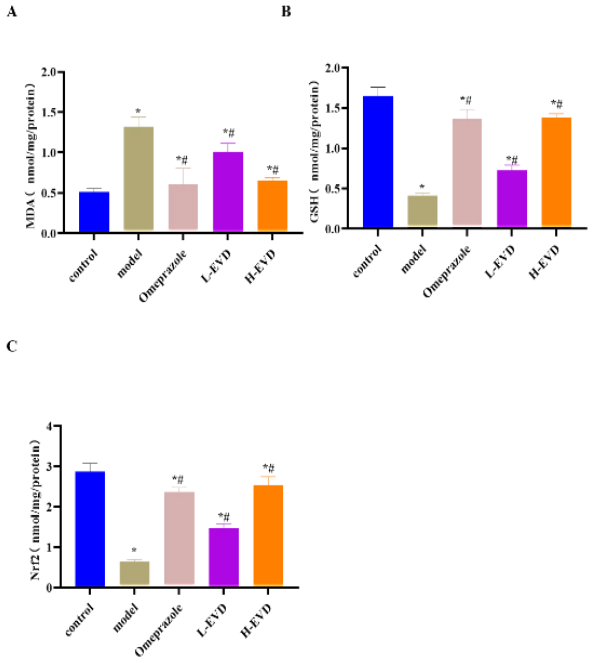

Figure 2: Evaluation of oxidative biomarkers. (A) Malondialdehyde (MDA) levels; (B) Reduced glutathione (GSH) levels; (C) Nrf2 levels. *P < 0.05 vs control group, $^{\#}p$ < 0.05 vs model group

Inflammatory biomarkers (TNF-α, IL-1β, MPO and ICAM-1)

Model group showed significant increase in TNF-α, IL-1β, MPO and ICAM-1 level compared to control group. However, omeprazole, low-dose evodiamine, and high dose evodiamine groups showed significant reduction in levels of pro-inflammatory biomarkers in gastric tissue when compared to model group (Figure 3).

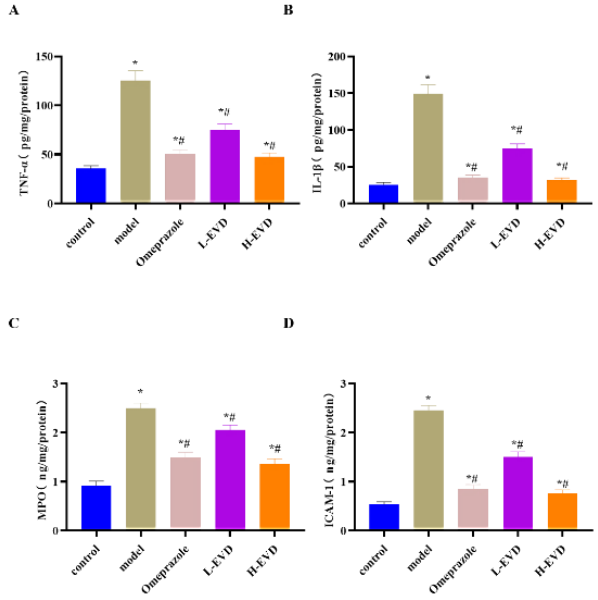

Figure 3: Evaluation of inflammatory biomarkers. (A) Tumor necrotic factor α (TNF-α) levels; (B) Interleukin 1β (IL-1β) levels; (C) myeloperoxidase (MPO) levels; (D) intracellular adhesion molecule-1 (ICAM-1) levels. *P < 0.05 vs control group, $^{\#}p$ < 0.05 vs model group

Histopathological examination of rats' gastric tissue

In control group, there were no hemorrhagic lesions or mucosal erosions observed. However, in the model group, the gastric lesions exhibited significant exacerbation, manifesting as severe mucosal damage with notable ruptures on gastric epithelial surface. The omeprazole, low-dose evodiamine, and high dose evodiamine groups showed mild mucosal damage with fewer ruptures on gastric epithelial surface (Figure 4 A).

The histological analysis using H & E staining revealed intact gastric structures such as the mucosa, muscularis mucosae and submucosa in control group. The model group showed significant mucosal damage, characterized by degeneration, superficial epithelial layer erosion and deep mucosal destruction. Edema, hemorrhage and inflammatory cells were also observed in the gastric mucosa. However, the

omeprazole, low-dose, and high dose evodiamine groups showed mild damage to the gastric mucosal epithelium, with no significant edema and mild infiltration of inflammatory cells (Figure 4 B). These findings suggest that evodiamine demonstrates a dose-dependent protective effect on gastric tissue.

DISCUSSION

Peptic ulcer is one of the most pervasive gastrointestinal diseases which affects 4–5% of people in society [10]. The gastric ulcer is characterized by the reduction in blood flow, infiltration of neutrophils, induction of oxidative stress and secretion of inflammatory cytokines. Various factors have been implicated in the development of gastric ulcers such as helicobacter pylori infection, alcohol consumption, smoking, excessive use of non-steroidal anti-inflammatory drugs (NSAIDs), and psychological and physiological stress. Nrf2 (NF-E2-related factor 2), a member of the Cap'n'collar (CNC) transcription factor family, consists of 605 amino acids and plays several roles in inflammatory processes.

Accumulating evidence suggests that Nrf2 counteracts the NF-κB-driven inflammatory response by competing with transcription co-activator cAMP response element (CREB) binding protein (CBP). In another study, Upregulation of Nrf2 inhibits the TNF-α-induced ICAM-1 expression in human retinal pigment epithelial cells treated with lycopene. All these studies suggest that Nrf2 plays a key role in the inflammatory process by regulating the migration and infiltration of inflammatory cells to inflamed tissue. Therefore, this study was aimed at investigating the effect of evodiamine on the signaling pathway of ROS/ICAM-1/Nrf2 in rats with acetic acid-induced stomach ulcers.

Reactive oxygen species (ROS) are generated in various compartments within cells and have diverse origins, either natural or as a result of toxic or pathological injuries. Prior studies have presented data indicating that ethanol exposure stimulates the production of ROS, leading to gastric damage. Consequently, enhancing antioxidant signaling pathways contributes to the protection against ulceration in the gastric mucosa. Consistent with previous studies, the findings indicated that the administration of acetic acid in the gastric tissue of rats led to significantly increased levels of MDA and decreased levels of GSH and Nrf2. To maintain redox homeostasis within cells, ROS are balanced through complex antioxidant mechanisms. Low-molecular-weight antioxidants, such as glutathione, play important roles as antioxidants. Nrf2 is promptly activated in response to intrinsic or extrinsic cellular stimuli that necessitate cellular defense mechanisms, such as oxidative injury or inflammation [11].

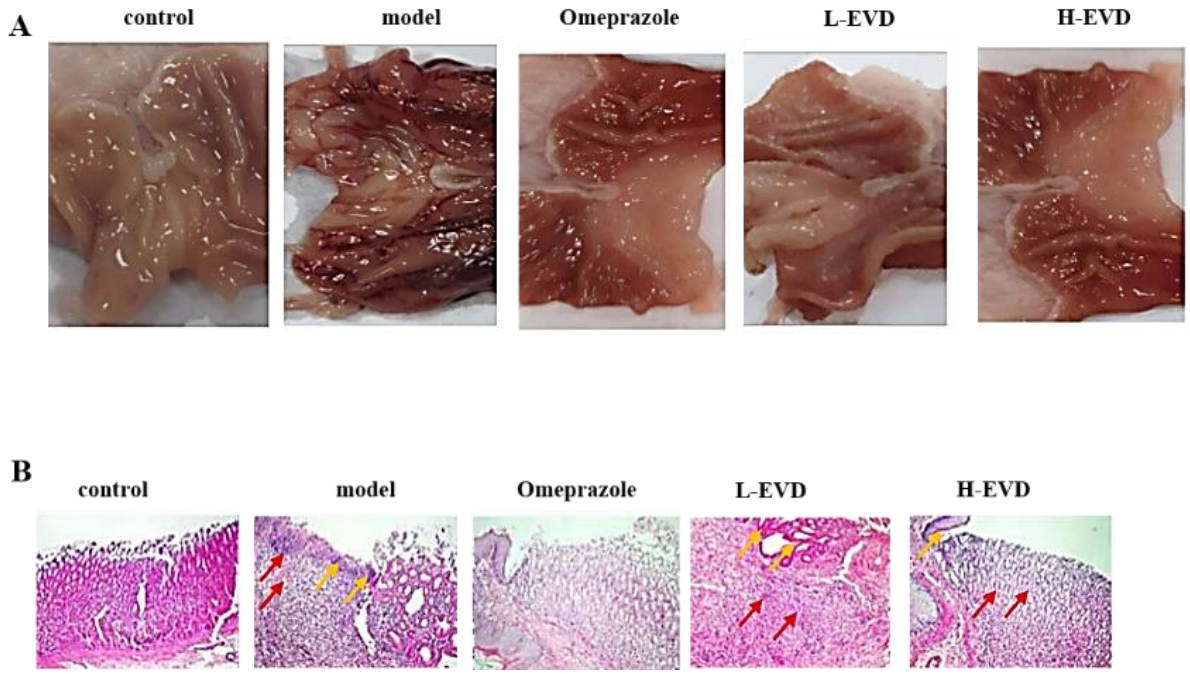

Figure 4: Histopathological examination of gastric tissue. (A) Microscopic images of the gastric tissues; (B) H & E staining results (Arrows indicated architectural changes)

Administration of low-dose and high dose evodiamine led to significant reduction in MDA and an increase in GSH levels and Nrf2 expression. Previous studies have demonstrated that evodiamine inhibits oxidative stress and prevents traumatic brain injury through the PGK1/NRF2 pathway. Evodiamine additionally suppresses the growth of rat vascular smooth muscle cells stimulated by PDGF-BB, by impeding cell proliferation and attenuating oxidative stress. These findings suggest that evodiamine may alleviate acetic acid-induced gastric ulcers by regulating oxidative stress.

Cellular cytokines are small proteins and peptides that play important roles in regulating cell development, differentiation, immune function, inflammation and wound healing. Interleukins (ILs), interferons, TNF, MPO and ICAM-1 are commonly used as markers for cellular cytokines [12]. When exposed to cytokines (due to an overwhelming presence of reactive oxygen species), target cells undergo oxidative injury. Oxidative stress-induced stimulation of NF-κB results in an overproduction of various pro-inflammatory cytokines. Moreover, the pro-inflammatory consequences of oxidative burden result in heightened NF-κB activation and cytokine synthesis [13].

Myeloperoxidase (MPO) is a key enzyme involved in inflammation and oxidative stress, making it a promising target for therapeutic interventions. It is predominantly present in infiltrating neutrophils and its activation triggers the generation of ROS and modulates pathways associated with inflammation [14]. Intracellular adhesion molecule-1 (ICAM-1) is commonly observed in inflamed sites and plays pivotal roles in regulating cellular interactions and inflammatory reactions. The importance of leukocyte adhesion in the initiation and maintenance of inflammation has been well-established in various animal experimental models [15]. The findings of this study revealed that administration of acetic acid significantly increases concentrations of pro-inflammatory cytokines (TNF-α, IL-1β, MPO and ICAM-1), in tandem with earlier findings [16]. Treatment with evodiamine resulted in significantly lower concentrations of TNF-α, IL-1β, MPO and ICAM-1 in a dose-dependent manner.

The findings from this investigation further suggest that the impact of evodiamine becomes more pronounced as the dose increases and the anti-inflammatory effects of evodiamine may be associated with upregulation of Nrf2. Earlier studies has shown that the overexpression of Nrf2 suppresses ICAM-1 induction by TNF-α in human retinal pigment epithelial cells [17]. Results of this study revealed that acetic acid administration (0.3 mL/rat) orally worsened gastric lesions, as evidenced by histopathological alterations such as degeneration, erosion of the gastric mucosal epithelium and damage to the deeper mucosal layer. Furthermore, the gastric mucosa exhibited signs of edema, hemorrhage and infiltration of inflammatory cells. Treatment with evodiamine for 15 days significantly improved gastric mucosal lesions and alleviated histopathological changes. These results align with a recent investigation conducted by Wang *et al* [18].

CONCLUSION

Evodiamine reduces oxidative stress, suppresses inflammatory reactions, and exerts anti-ulcer effect on acetic acid-induced gastric ulcers in rats by targeting the ROS/ICAM-1/Nrf2 signaling pathway. There is need for additional studies into the integration of evodiamine into conventional pharmaceutical treatments for gastric ulcers, indicating its potential antioxidant and anti-inflammatory effects through the ROS/ICAM-1/Nrf2 signaling pathway.

DECLARATIONS

Acknowledgement

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Funding

None provided.

Ethical approval

It was granted by Animal Care and Use Review Committee of Affiliated Haikou Hospital of Xiangya Medical School, Central South University (HK-XY-021).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities

pertaining to claims relating to the content of this article will be borne by them.

REFERENCES

1. *Dong Z, Zhang X, Chen X, Zhang J. Significance of serological gastric biopsy in different gastric mucosal lesions: An observational study. Clin Lab 2019; 65(12).*
2. *Shen Y, Sun J, Niu C, Yu D, Chen Z, Cong W, Geng F. Mechanistic evaluation of gastroprotective effects of Kangfuxin on ethanol-induced gastric ulcer in mice. Chem-Biol Interact 2017; 273: 115-124.*
3. *Devaraj VC, Gopala KB, Viswanatha GL, Satya PV, Vinay BS. Protective effect of leaves of Raphinus sativus Linn on experimentally induced gastric ulcers in rats. Saudi Pharm J 2011; 19(3): 171-176.*
4. *Mairuae N, Buranrat B.Cheepsunthorn P. Crude extracts of Momordica cochinchinensis (Lour.) Spreng exerts antioxidant and anti-neuroinflammatory properties in LPS-stimulated BV2 microglia. Trop J Pharm Res 2024; 23(1): 91-97 doi: 10.4314/tjpr.v23i1.12*
5. *Kangwan N, Park JM, Kim EH, Hahm KB. Quality of healing of gastric ulcers: Natural products beyond acid suppression. World J Gastrointest Pathophysiol 2014; 5(1): 40-47.*
6. *Jiang ZB, Huang JM, Xie YJ, Zhang YZ, Chang C, Lai HL, Wang W, Yao XJ, Fan XX, Wu QB, et al. Evodiamine suppresses non-small cell lung cancer by elevating CD8(+) T cells and downregulating the MUC1-C/PD-L1 axis. J Exp Clin Canc Res 2020; 39(1): 249.*
7. *National Research Council. Guide for the care and use of laboratory animals, National Academies Press. Washington, DC; 2010.*
8. *Jiang DF, Zhang XG, Yang HL, Sun C. Differential expression of lipid metabolism genes in the liver and adipose tissue of mice treated with evodiamine. Genet Mol Res 2013; 12(2): 1501-1510.*
9. *Abdel-Aziz SA, Taher ES, Lan P, Asaad GF, Gomaa H, El-Koussi NA, Youssif B. Design, synthesis and biological evaluation of new pyrimidine-5-carbonitrile derivatives bearing 1,3-thiazole moiety as novel anti-inflammatory EGFR inhibitors with cardiac safety profile. Bioorg Chem 2021; 111: 104890.*
10. *Aihara T, Nakamura E, Amagase K, Tomita K, Fujishita T, Furutani K, Okabe S. Pharmacological control of gastric acid secretion for the treatment of acid-related peptic disease: past, present, and future. Pharmacol Ther 2003; 98(1): 109-127.*
11. *Xu C, Song Y, Wang Z, Jiang J, Piao Y, Li L, Jin S, Li L, Zhu L, Yan G. Pterostilbene suppresses oxidative stress and allergic airway inflammation through AMPK/Sirt1 and Nrf2/HO-1 pathways. Immun Inflamm Dis 2021; 9(4): 1406-1417.*
12. *Saha S, Buttari B, Panieri E, Profumo E, Saso L. An overview of Nrf2 signaling pathway and its role in inflammation. Molecules 2020; 25(22): 5474*
13. *Bellezza I, Giambanco I, Minelli A, Donato R. Nrf2-Keap1 signaling in oxidative and reductive stress. Bba-Mol Cell Res 2018; 1865(5): 721-733.*
14. *Chen S, Chen H, Du Q, Shen J. Targeting myeloperoxidase (MPO) mediated oxidative stress and inflammation for reducing brain ischemia injury: Potential application of natural compounds. Front Physiol 2020; 11: 433.*
15. *Bui TM, Wiesolek HL, Sumagin R. ICAM-1: A master regulator of cellular responses in inflammation, injury resolution and tumorigenesis. J Leukocyte Biol 2020; 108(3): 787-799.*
16. *Mohamed NI, Suddek GM, El-Kashef DH. Molsidomine alleviates acetic acid-induced colitis in rats by reducing oxidative stress, inflammation and apoptosis. Int Immunopharmacol 2021; 99: 108005.*
17. *Yang PM, Wu ZZ, Zhang YQ, Wung BS. Lycopene inhibits ICAM-1 expression and NF-kappaB activation by Nrf2-regulated cell redox state in human retinal pigment epithelial cells. Life Sci 2016; 155: 94-101.*
18. *Wang C, Yuan Y, Pan H, Hsu AC, Chen J, Liu J, Li P, Wang F. Protective effect of ocotillol, the derivate of ocotillol-type saponins in Panax Genus, against acetic acid-induced gastric ulcer in rats based on untargeted metabolomics. Int J Mol Sci 2020; 21(7): 2577.*