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ORIGINAL ARTICLE

Protective Effect of Crataegus Hydroalcoholic Extract on Intestinal Ischemia-Reperfusion Injury in a Rat Model

Hamid Akbari^{1*}, Porya Mohajeri², Siamak Kazemi-Darabadi¹, Javad Ashrafi-Helan³,
Abolfazl Alirezalu⁴

¹ Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran.

² Graduated of Veterinary Medicine, Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran.

³ Department of Pathobiology, Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran.

⁴ Department of Horticultural Sciences, Faculty of Agriculture, Urmia University, Urmia, Iran.

Abstract

Objective- This study examined the effect of Crataegus hydroalcoholic extract (CHE) on intestinal ischemia-reperfusion (I/R) in rats.

Design- Experimental study

Animals- 25 adult male Wistar rats

Procedures- Rats weighing 200 ± 25 g were randomly divided into five individual groups as follows: sham group without intestinal I/R, control group with intestinal I/R, and treatment groups with intestinal I/R and 10 days oral administration of CHE at doses of 25, 50 and 100 mg/kg. Intestinal I/R was accomplished by occlusion of the cranial mesenteric artery for 30 min, followed by 60 min reperfusion. Then tissue sections of jejunum were prepared and stained with hematoxylin-eosin. Histopathological lesions including hyperemia, hemorrhage, necrohemorrhagic inflammation, and villi destruction were scored as mild, moderate and severe.

Results- In histopathologic evaluation, sham and control group showed the minimum and maximum injury, respectively. The mean scores of necrohemorrhagic inflammation and villi destruction significantly decreased in 25 mg/kg CHE group compared to control. However, hyperemia and hemorrhage did not change in comparison to control ($p > 0.007$). In the group of 50 mg/kg CHE, no pathologic lesions were observed and the results were similar to those in the sham group. The mean scores of hyperemia and necrohemorrhagic inflammation in the 100 mg/kg CHE group had no significant difference with the control group. However, the mean rank of hemorrhage and villi destruction was significantly lower than control and higher than the sham group ($p < 0.007$).

Conclusion and clinical relevance- The findings of this study indicate that CHE at the dose of 50 mg/kg has the most protective effect against intestinal I/R injury in a rat model. Therefore, Crataegus can be a promising compound against intestinal I/R injuries.

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* Correspondence to: Hamid Akbari, Department of Clinical Sciences, Faculty of Veterinary Medicine, University of Tabriz, Tabriz, Iran. E-mail: h.akbari@tabrizu.ac.ir



1. Introduction

Ischemia/reperfusion (I/R) injury is a major concern in situations such as mechanical and strangulating obstructions, severe trauma, coagulopathies,^{1,2} strangulated hernias, severe burns, septic, and hypovolemic shock.³ Ischemic injury occurs after interruption of blood flow to an organ leading to cellular necrosis. Paradoxically, reperfusion happens after restoration of blood supply that causes additional injury, this event is called I/R injury.³ The mucosal surface of the small intestine is covered with villi which is damaged in ischemic conditions due to lack of oxygen in villus epithelium.⁴ After reperfusion in injured sites, radical oxygen species (ROS) and proteases releases and a massive invasion of neutrophil occurs to the site.⁵

Neutrophils exacerbate damage by releasing cytotoxic free radicals and proteolytic enzymes. Free radicals can destroy cell membranes and subcellular structures that contain high levels of phospholipid and protein, causing peroxidation of lipids and structural changes that result in cell apoptosis and necrosis.⁶

The harmful effects of ROS on the intestinal tissue can be eliminated by antioxidant compounds. *Crataegus* spp. belongs to the Rosaceae family, which has 150 to 1200 species, and is commonly distributed in temperate regions of the Northern hemisphere.⁷ The major constituents of *Crataegus* species are flavonoids, oligomeric proanthocyanidins (OPCs) and some phenolic acids which are well-known for their antioxidant properties.⁷ Many studies have been shown that *Crataegus* extract is effective in scavenging ROS, particularly free radicals and it is valuable natural compound for treating different kinds of I/R injuries in brain⁸ and heart.⁹⁻¹² However, it has not been used for treating intestinal I/R.

Therefore, the present study was aimed to evaluate the protective effect of *Crataegus* hydroalcoholic extract (CHE) on the intestinal I/R injury in rats by assessing histopathologic changes including, hyperemia,

hemorrhage, necrohemorrhagic inflammation and villi destruction in the epithelium of small intestines.

2. Materials and Methods

Animals

25 adult male Wistar rats weighing 200±25 g were randomly divided into five individual groups and kept in a place with 22° C temperature, 40-70% humidity, and 12-hour light/dark cycle. All of the animals had free access to water and food pellets. The animals had one week of adaptation period, then were gavaged with a certain dosage of CHE or only normal saline depending on groups for 10 days. Treated groups were gavaged with different doses of CHE (25, 50, and 100 mg/kg) and untreated groups (Sham and Control) gavaged with 1 ml normal saline.

Preparation of Crataegus extract and HPLC analysis

For preparing *Crataegus* hydroalcoholic extract, first the flowers and leaves of hawthorn were dried and milled; then, one gram of powdered mixture was mixed with 80% methanol then placed in a 25° C sonic instrument for 15 minutes. The solution was passed through a filter paper and its volume was measured. After refolding the samples with the filter, they were poured into small HPLC glass containers and kept refrigerated until use. In this analysis, flavonoids quercetin, isoquercetin, rutin, vitexin, vitexin ramnozide, hyporosid, as well as high purity chlorogenic acid were used as standard. Preparation of the standard solution at 5, 10, 25, 50, 100, 250, and 500 ppm was taken place to plot the calibration curve of the HPLC apparatus. 10 µL of prepared Standard specimens and extracts for measuring flavonoids and chlorogenic acid were injected into an HPLC apparatus. The method used in this study was gradient. Movable phase A contained water (99.95%) and formic acid (0.05%) and mobile phase B contained methanol (20%) and acetonitrile (80%). The moving phase

speed was 1 ml/min and the maximum absorbance wavelength was 400 nm. Choosing the right wavelength is one of the things that should be considered. Considering measuring different compounds, 320 nm (chlorogenic acid), 335 nm (vitexin ramenozid and vitexin) and 360 nm (routine, hyporeside, isococetin and quercetin) used for measuring these components.

Intestinal I/R technique

16-18 hours prior to surgery animals didn't take any food but had free access to water¹³ and then took 50 mg/kg ketamine and 5 mg/kg xylazine for anesthesia.¹⁴ After aseptic preparation of ventral midline, celiotomy was performed. Cranial mesenteric artery (CMA) was detected and occluded with atraumatic microvascular clamp for 30 minutes (ischemic phase) then the clamp was removed for one hour (reperfusion phase) (Figure 1). Segments of the ileum (about 2 cm in length) were harvested and after cleansing with normal saline placed in cold 10% buffered formalin containers then rats were euthanized after taking blood samples. All of the groups had intestinal I/R except sham group which only had isolation of CMA without occlusion.

Histopathological study

After regular tissue processing, samples were placed into paraffin blocks and cut into 5 µm slices. Sample sections



Figure 1. Temporary ischemia in the anterior mesenteric artery.

were stained with hematoxylin-eosin and studied by a pathologist under a light microscope without previous knowledge about the sections. In each section, pathologic lesions such as hyperemia, hemorrhage, necrohemorrhagic inflammation, and villi destruction were classified into four grade including none (grade 0), mild (grade 1), moderate (grade 2) and severe (grade 3). Criteria for the classification of pathologic lesions are shown in Table 1.

Statistical analysis

Data were analyzed using SPSS version 21 statistical software (IBM Corp., Armonk, NY. USA). The Kruskal-Wallis test was used to determine significant differences in the mean scores of histopathologic lesions including hyperemia, hemorrhage, necrohemorrhagic inflammation, and villi destruction among all treatments. A *p*-value of less than 0.05 was considered significant. Mann-Whitney tests were used as post hoc tests with a Bonferroni correction and a critical value for significance at *p*<0.007.

3. Results

HPLC analysis

The injected standards into the HPLC apparatus, such as chlorogenic acid, quercetin, isoquercetin, routine, vitexin, vitexin ramenozide, and hyporosid were shown in Figure 2. The HPLC analysis of CHE indicated that the flavonoids including chlorogenic acid, vitexin ramenozide and vitexin were the main constituents of CHE.

Histopathologic results

Hematoxylin-eosin staining was carried out to determine the histological changes of the small intestine. In the sham operated group, no histological lesions were observed (Figure 3a). In the control group, severe hyperemia, epithelial necrosis which extended to the lamina propria, severe inflammation with extensive neutrophil infiltration

Table 1: The criteria for classification of histopathologic lesions in small intestines

Severity	Hyperemia	Hemorrhage	Necrohemorrhagic inflammation	Villi destruction
None (grade 0)	None	None	None	None
Mild (grade 1)	Relative dilation in some capillaries and need to change the field of the microscope to see the hyperemic blood vessels.	Focal hemorrhages scattered that need to change the microscope field to see the next foci	Hemorrhage and destruction foci scattered	Destruction of the tip of some villi (less than 50% length of villi)
Moderate (grade 2)	Relative dilation of all capillaries	At least one or more focal hemorrhages were seen in each field of microscope	Hemorrhage and destruction foci were seen in each field of microscope	Destruction of the tip of all villi (less than 50% length of villi)
Severe (grade 3)	All capillaries, arterioles and venules are completely dilated with erythrocytes (vasodilation)	Extensive hemorrhages in all layer of small intestine	Extensive hemorrhages and destruction with infiltration of mononuclear and polymorphonuclear cells	Complete destruction of villi epithelium sometimes extended to the lamina propria

between normal and necrotic tissues and subserosal hemorrhages were observed (Figure 3b). In histopathologic sections prepared from the small intestines of rats that received 25 mg/kg of CHE, mild destruction of villi, shortening of villi heights as well as moderate hyperemia and mild focal hemorrhage were observed (Figure 3c). In the group receiving the CHE at a dose of 50 mg/kg, a minimum of pathologic lesions was observed. The microscopic images of the intestine were very similar to the sham group and, except for mild hyperemia, no other lesion was seen (Figure 3d). However, there were relatively severe lesions including destruction and shortening of villi, hyperemia, hemorrhage and moderate necrohemorrhagic inflammation in rats receiving 100 mg/kg of CHE (Figure 3e). In addition, according to the classification of histopathologic lesions in Table 1, the least pathologic damage was observed in the group received 50 mg/kg of CHE.

The Mean rank of histopathologic lesions in the small intestine of all treatment groups was demonstrated in Table 2. A Kruskal-Wallis test for histopathological data showed that there was a statistically significant difference in hyperemia, hemorrhage, necrohemorrhagic inflammation and villi destruction scores between the different treatments ($p < 0.001$). Mann-Whitney post hoc tests

indicated that the severity of lesions in the control group was significantly higher than the sham group in all of the evaluated parameters.

The mean scores of necrohemorrhagic inflammation and villi destruction in the group received 25 mg/kg of CHE were significantly lower than control. However, in this group no significant difference was observed in hyperemia and hemorrhage scores compared to control (Figures 4-7). In the 50 mg/kg CHE group, the mean scores of all pathologic parameters were significantly lower than that of the control group. In addition, the parameters mentioned in this group did not differ significantly with the sham group. The mean scores of hyperemia and necrohemorrhagic

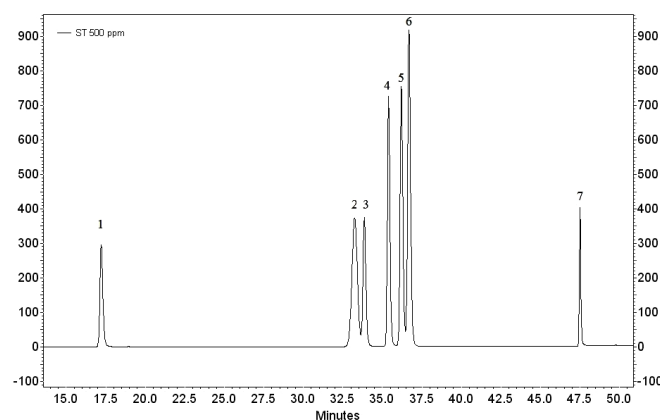


Figure 2. The injected standards into the HPLC apparatus, 1: chlorogenic acid, 2: vitexin ramenoizide, 3: vitexin, 4: routine, 5: hyporosid, 6: isoquerstin, 7: quercetin.

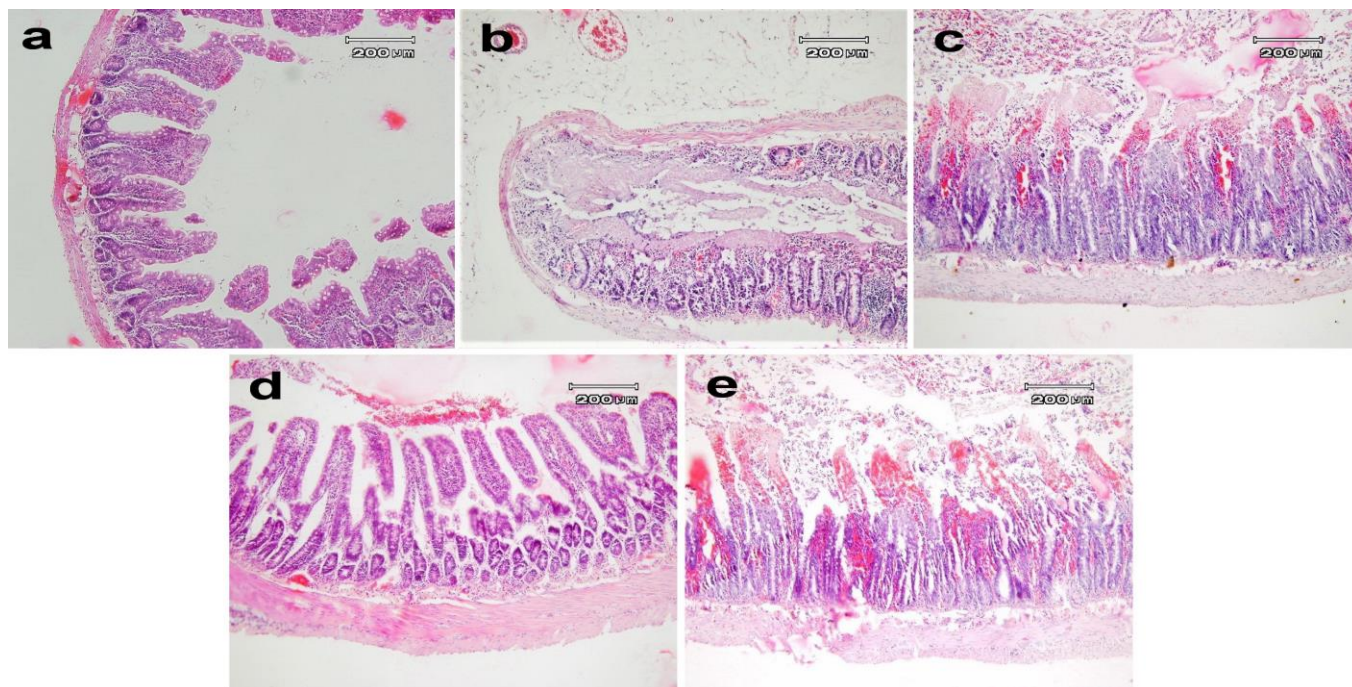


Figure 3. **a:** Normal small intestine of rats in sham group. **b:** Ischemia/reperfusion in the small intestine of rat in control group. Severe arterial congestion, subserosal hemorrhage, and destruction of intestinal mucosa with fibrinonecrotic inflammation. **c:** Hemorrhagic foci and destruction of the tip of some villi (mild necrosis) in 25 mg/kg CHE group. **d:** Histopathological section of 50 mg/kg CHE group, mild hyperemia, very similar to sham group. **e:** Severe hyperemia and moderate villi destruction (necrosis) in 100 mg/kg CHE group. (H&E).

Table 2: The Mean rank of histopathologic lesions in the small intestine of all treatment groups

Groups	Hyperemia*	Hemorrhage*	Necrohemorrhagic inflammation*	Villi destruction*
Sham	3	5.5	6	5.5
Control	20	22.5	22.5	23
CHE 25 mg/kg	13.5	15.5	12.8	15.5
CHE 50 mg/kg	8.5	5.5	6	5.5
CHE 100 mg/kg	20	16	17.7	15.5
Chi-square (df)	22.59 (4)	22.33 (4)	21.71 (4)	24 (4)

* A Kruskal-Wallis test showed that there was a significant difference among treatment groups; $p < 0.001$.

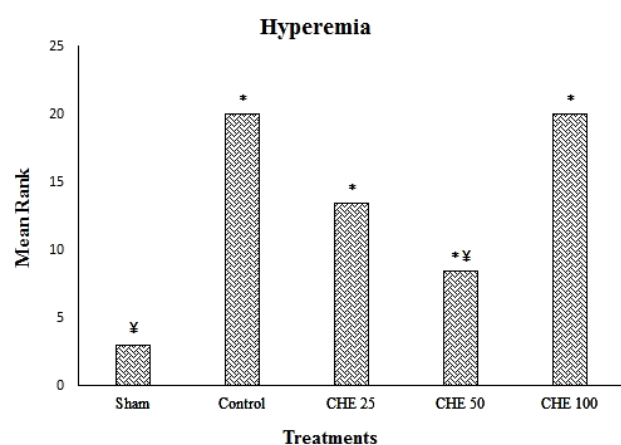


Figure 4: The mean rank of hyperemia among all treatment group. * indicates significant differences ($p < 0.007$) compared to sham group. ¥ indicates significant differences ($p < 0.007$) compared to control group.

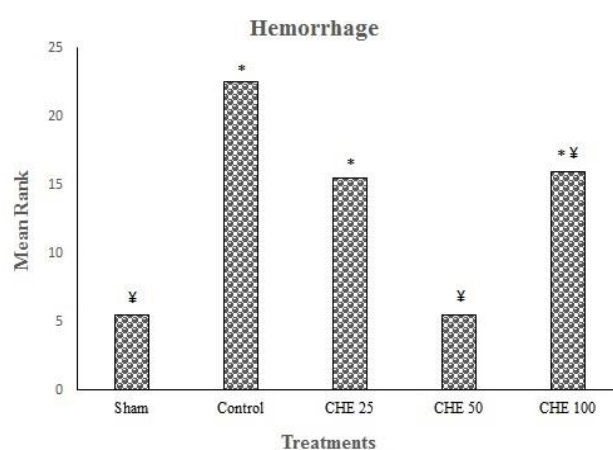


Figure 5: The mean rank of hemorrhage among all treatment group. * indicates significant differences ($p < 0.007$) compared to sham group. ¥ indicates significant differences ($p < 0.007$) compared to control group.

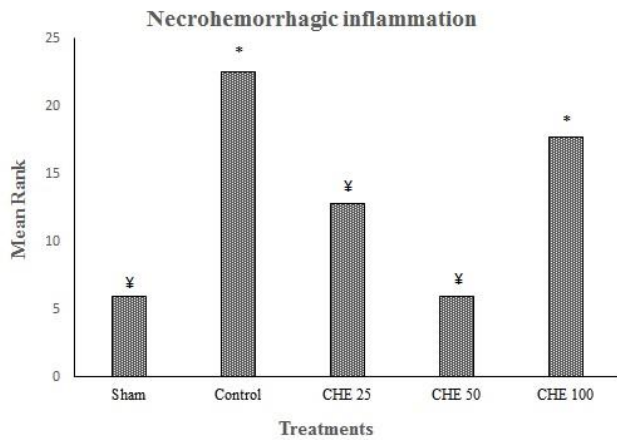


Figure 6: The mean rank of necrohemorrhagic inflammation among all treatment group. * indicates significant differences ($p < 0.007$) compared to sham group. ¥ indicates significant differences ($p < 0.007$) compared to control group.

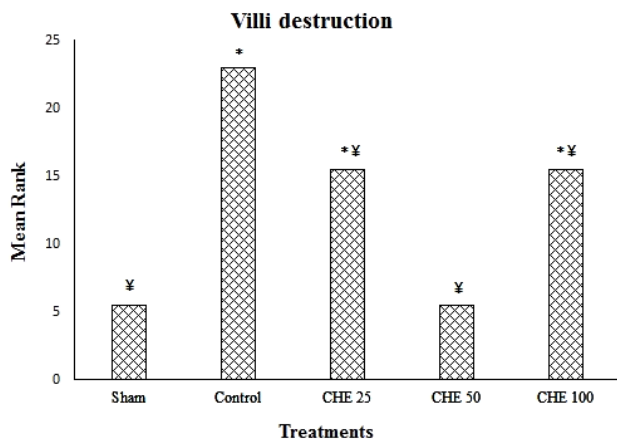


Figure 7: The mean rank of villi destruction among all treatment group. * indicates significant differences ($p < 0.007$) compared to sham group. ¥ indicates significant differences ($p < 0.007$) compared to control group.

inflammation in the 100 mg/kg CHE group had no significant difference with the control group. However, the mean rank of hemorrhage and villi destruction was significantly lower than the control group, although it had higher values than the sham group ($p > 0.007$).

4. Discussion

Ischemia/reperfusion injury in the small intestine is an important and complex problem caused by intestinal obstruction, trauma, hemorrhagic shock, and septicemia.^{1,2,15} Many studies have been conducted to find effective compounds for reducing the damage caused by

I/R in the intestine, but a definitive therapeutic approach has not yet been found. One of the common methods used to investigate the intestinal I/R injury is the histopathological examination of small intestine tissue. Therefore, this study investigated the protective effects of Crataegus extract using this method in a rat model. The results of this study suggest that Crataegus can be a promising compound against intestinal I/R injury.

Our data showed that there was no histopathologic lesion in the sham group. However, in the control group, there was severe hyperemia, loss of villous epithelium, epithelial necrosis, inflammatory cell infiltration, and hemorrhage into the intestinal wall. These results are consistent with previous studies reported by other researchers on intestinal I/R injuries in animals.^{16,17} I/R injury caused by inadequate blood supply to the intestinal tissue, and consequently the production of free oxygen radicals, cytokines, leukocyte infiltration, especially neutrophils, and the release of inflammatory mediators.^{3,18} Two of the major events that cause pathophysiological disorders in I/R injury are the neutrophil invasion and release of free oxygen radicals.^{3,10,16} Previous studies have shown that Crataegus extract has strong antioxidant properties and is capable of inhibiting neutrophil elastase activity.¹⁰ These effects are produced by OPCs which are one of the main constituents of Crataegus.⁷ In many studies, the antioxidant properties of Crataegus are attributed to its phenolic compounds.^{7,12,19} Tadić *et al.*²⁰ demonstrated that the antioxidant and anti-inflammatory effects of Crataegus are related to flavonoids. In the present study, the HPLC analysis of Crataegus extract exhibited that flavonoids such as chlorogenic acid, vitexin ramnozide, and vitexin had the highest concentrations. It has been shown that chlorogenic acid has a protective effect on the I/R injury of the brain in rats by various mechanisms such as reduction of inflammatory mediators and cytokines.²¹ Furthermore, its protective effect has been demonstrated on I/R-induced liver injury by inhibition of inflammatory response and improvement of antioxidant defense systems.²² Also, the

protective effect of vitexin has been shown on I/R-induced injury to brain and myocardium, and the prevention or delay in inflammatory responses and cell apoptosis are referred to as protective mechanisms.²³⁻²⁶ Another mechanism for protecting the body against I/R injury is the enhanced synthesis of endothelial nitric oxide.²⁷ In a study has been exhibited that Crataegus extract improved I/R-induced injury in myocardium through this mechanism.¹⁰ In this study, the effect of orally administered CHE at the doses of 25, 50, and 100 mg/kg for 10 consecutive days was evaluated on intestinal I/R injury. The results showed that administration of CHE at dose of 25 mg/kg improved necrohemorrhagic inflammation and villi destruction. No pathologic lesion was observed other than mild hyperemia in the 50 mg/kg of CHE. Although hyperemia and necrohemorrhagic inflammation were greater in the dose of 100 mg/kg, the intensity of hemorrhage and villi destruction was significantly lower than the control group. However, the intensity of these parameters was significantly higher than the sham group. So, it can be said that the protective effect of CHE decreased at the dose of 100 mg/kg. Contrary to expectations, this study did not find a dose-dependent effect in Crataegus extract against intestinal I/R injury, despite the effect of the extract was dose-dependent up to the dose of 50 mg/kg. In contrast to our study results, hawthorn extract produced dose-dependent gastroprotective activity in ethanol-induced acute stress ulcer model in rat.²⁰ In another study, the protective effect of orally administered hawthorn extract at doses of 10 and 100 mg/kg was investigated on myocardial I/R injury and a dose-dependent effect was found.¹⁰ This discrepancy may be due to the study on different tissues or duration of extract used. However, it seems that the results of this study are not sufficient to confirm whether the effect of Crataegus extract on intestinal I/R injury is dose dependent or not. Further research on different doses of the extract is required to establish this. In general, the results of this study showed that Crataegus extract at the dose of 50 mg/kg effectively reduces intestinal I/R injury in rats.

Acknowledgment

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Conflict of interest

The authors declare that they have no conflict of interest.

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چکیده

اثر حفاظتی عصاره هیدرو الکلی زالزالک بر روی آسیب ایسکمی/پرفیوژن مجدد روده در مدل حیوانی
موش صحرایی

حمید اکبری^۱، پوریا مهاجری^۲، سیامک کاظمی درآبادی^۱، جواد اشرفی هلان^۳، ابوالفضل علیرضالو^۴

^۱ گروه علوم درمانگاهی، دانشکده دامپزشکی، دانشگاه تبریز، تبریز، ایران.

^۲ دانش‌آموخته دامپزشکی، دانشکده دامپزشکی، دانشگاه تبریز، تبریز، ایران.

^۳ گروه پاتوبیولوژی، دانشکده دامپزشکی، دانشگاه تبریز، تبریز، ایران.

^۴ گروه علوم باغبانی، دانشکده کشاورزی، دانشگاه ارومیه، ارومیه، ایران.

هدف: در این مطالعه اثر عصاره هیدرو الکلی زالزالک بر روی آسیب ایسکمی/پرفیوژن مجدد روده موش صحرایی بررسی گردید.

طرح مطالعه: مطالعه تجربی

حیوانات: تعداد ۲۵ سر موش صحرایی نژاد ویستار

روش کار: موش‌های صحرایی با وزن تقریبی 25 ± 200 گرم به صورت تصادفی در ۵ گروه جداگانه بدین ترتیب تقسیم‌بندی شدند: گروه شم بدون انجام ایسکمی/پرفیوژن مجدد، گروه کنترل با انجام ایسکمی/پرفیوژن مجدد، گروه‌های درمانی عصاره هیدرو الکلی زالزالک در دوزهای ۲۵، ۵۰ و ۱۰۰ میلی گرم بر کیلوگرم وزن بدن به مدت ۱۰ روز با تجویز خوراکی همراه با انجام ایسکمی/پرفیوژن مجدد. ایسکمی/پرفیوژن مجدد با مسدود کردن شریان مزانتریک قدامی به مدت ۳۰ دقیقه و سپس پرفیوژن مجدد به مدت ۶۰ دقیقه انجام شد. سپس مقاطع بافتی از ژژنوم تهیه شده و با هماتوکسیلین-اؤزین رنگ آمیزی شدند. ضایعات هیستوپاتولوژیک شامل پرخونی، خونریزی، التهاب نکروهمورائیک و تخریب پرزهای روده به درجات خفیف، متوسط و شدید تقسیم‌بندی شدند.

نتایج: در بررسی‌های پاتولوژیک گروه شم کمترین و گروه کنترل بیشترین آسیب را داشتند. در گروه ۲۵ میلی گرم بر کیلوگرم عصاره هیدرو الکلی زالزالک، میانگین درجات فاکتورهای التهاب نکروهمورائیک و تخریب پرزها به صورت معناداری نسبت به گروه کنترل کاهش یافت. درحالی که میزان پرخونی و خونریزی نسبت به گروه کنترل تغییر معناداری نداشت ($p > 0.007$). در گروه ۵۰ میلی گرم بر کیلوگرم عصاره هیدرو الکلی زالزالک هیچ ضایعه پاتولوژیکی مشاهده نشد و نتایج مشابه گروه شم بود. میانگین رتبه‌های فاکتورهای پرخونی و التهاب نکروهمورائیک در گروه ۱۰۰ میلی گرم بر کیلوگرم عصاره هیدرو الکلی زالزالک تفاوت معناداری با گروه کنترل نداشت. اگرچه، میانگین رتبه‌های فاکتورهای خونریزی و تخریب پرزها به صورت معناداری کمتر از گروه کنترل و بیشتر از گروه شم بود ($p < 0.007$).

نتیجه‌گیری و کاربرد بالینی: یافته‌های مطالعه حاضر نشان دادند که عصاره هیدرو الکلی زالزالک در دوز ۵۰ میلی گرم بر کیلوگرم بیشترین اثرات حفاظتی را در برابر آسیب ناشی از ایسکمی/پرفیوژن مجدد روده در مدل حیوانی رت دارد؛ بنابراین زالزالک می‌تواند یک ماده امیدوارکننده در برابر آسیب‌های ناشی از ایسکمی/پرفیوژن مجدد روده باشد.

واژه‌های کلیدی: ایسکمی/پرفیوژن مجدد، زالزالک، عصاره هیدرو الکلی، روده