Animal models of cathartic colon

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Abstract

The incidence of cathartic colon has been increasing, but satisfactory treatments are still lacking. In order to study the pathological mechanisms of the disorder and identify effective treatment methods, researchers have established different animal models of cathartic colon. This minireview briefly summarizes several common cathartic colon animal models, induced with anthraquinone laxatives such as rhubarb, total anthraquinone, rhein, and emodin, or induced with diphenylmethane laxatives such as phenolphthalein. The advantages and limitations of these models are evaluated and analyzed. We hope that this review will facilitate the selection of suitable models and improve relevant modeling methods. We anticipate the development of more convenient and stable models that can reflect the characteristics of cathartic colon in humans, and serve as useful tools for further studies.

Key Words: Cathartic colon; Animal model; Laxative; Anthraquinones; Diphenylmethane; Constipation

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Core Tip: To our knowledge, this is the first review on various cathartic colon animal models. In this minireview, the experimental animals, agents, and methods frequently used to establish cathartic colon animal models are summarized for reference.

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INTRODUCTION

Cathartic colon is a common form of refractory functional constipation. It is characteristic of slow transit constipation (STC), typically characterized by long-term consumption of large doses of stimulating laxative drugs as the main pathogenic factor, and decreased colonic motility as the main pathological feature\(^5\). STC is also characterized by delayed colonic transit, difficulty in defecation caused by decreased colonic motility, and/or reduced frequency of defecation, and dry stools\(^6\). The condition is often accompanied by abdominal distension, abdominal pain, stomach pain, nausea, vomiting, and perianal diseases, as well as cardiovascular disease and colon cancer, and may seriously affect the quality of life\(^5\). In order to relieve symptoms, patients often rely on laxative defecation. Thus, the effects of the condition worsen, as the administered dose of laxatives is usually increased. Such a vicious cycle may lead to cathartic colon, with or without melanosis coli.

Although the pathological mechanisms of cathartic colon have not been discovered entirely, its main cause is the long-term overuse of laxatives. The main types of laxatives commonly used in clinical practice are: (1) Bulking or hydrophilic agents; (2) Osmotic agents; (3) Lubricants; and (4) Stimulants. The stimulants include anthraquinones (AQs), diphenylmethane, and their derivatives, which can stimulate the intestinal wall to increase intestinal motility, and are thought to be likely causes of cathartic colon\(^7\).

Treatment of cathartic colon is particularly difficult owing to the lack of more effective laxative drugs that do not aggravate cathartic colon, and the fact that patients with a severe condition may even require a colectomy to alleviate the symptoms. Understanding the pathological mechanisms of cathartic colon forms the basis of its prevention and treatment. Animal models are often required in related studies. This review attempts to summarize and evaluate existing cathartic colon animal models.

RECOGNITION OF CATHARTIC COLON

In 1943, Heilbrun\(^6\) first identified the main features of cathartic colon based on radiographic findings in a patient with STC, who had been using stimulant laxatives for a long period of time. The imaging findings included loss of haustration, pseudostrictures (that is, variable sandglass formed spasms), dilated lumen, dilated terminal ileum, and gaping of the ileocecal valve. Smith\(^7\) has since identified 12 cases of pathological and anatomical changes in the colons of laxative addicts, including three main features: (1) Loss of intrinsic innervation; (2) Atrophy of smooth muscle coats; and (3) Melanosis coli. Clain et al\(^8\) also found discrete linear ulcers and eosinophilic granulocyte infiltration in the cecum of one patient. Studies of the pathophysiology of the cathartic colon have been focused on the enteric nervous system, gastrointestinal hormones, and interstitial cells of Cajal. Although studies on cathartic colon have reported some useful results, the pathological mechanisms of the disease have still not been completely clarified, and treatment methods are unsatisfactory.

MODELING METHOD

Animal models used in studies of cathartic colon have been based mainly on methods first established in 1998 by Zhang et al\(^9\). Adult Wistar rats were selected, and half of the study animals were male. The rats were fed either rhubarb powder or phenolphthalein. The initial dose of rhubarb powder in the feed was 200 mg/kg/d, which was subsequently increased by 200 mg/kg/d. About half of the animals had loose stool when the dose was increased to 1000 mg/kg/d. This dosage was maintained until the loose stool was no longer evident. The dose was then again increased by 200 mg/kg/d. Thus, more than half of the animals had diarrhea for 3 mo. The final dose of rhubarb powder was 2600 mg/kg/d\(^9\). In the other experimental group, the initial dose of phenolphthalein was 200 mg/kg/d. The first median diarrheal dose (the dose that was able to induce diarrhea in half of the animals in the group) was 1600 mg/kg/d. The final adjusted dose was 3600 mg/kg/d\(^9\).

Based on the two aforementioned methods, various animal species and strains, drug types and doses, drug dosage increase over time, and administration methods were modified in the following studies (Table 1).
# Table 1 Summary of cathartic colon animal models

| Chemical                  | Initial/final dose (mg/kg/d) | Method of administration | Animals                                      | Molding cycle (d) | Melanosis coli | Ref. |
|---------------------------|------------------------------|--------------------------|----------------------------------------------|-------------------|----------------|------|
| Rhubarb                   | 100/3200                     | Drug-containing fodder   | Wistar rat, male and female                  | 30                | No             | [9]  |
|                           | 200/2400                     | Drug-containing fodder   | Wistar rat, male and female                  | 90                |                |      |
|                           | 200/3600                     | Drug-containing fodder   | Wistar rat, male and female                  | 90                |                |      |
|                           | 200/2600                     | Drug-containing fodder   | Wistar rat, male and female                  | 90                |                |      |
|                           | 200/2400                     | Gavage                   | SD rat, male and female                      | 84                |                | [43] |
|                           | 200/3200                     | Gavage                   | SD rat, male and female                      | 84                |                |      |
|                           | 300/3600                     | Drug-containing fodder   | Wistar rat, male                            | 136               |                | [21] |
|                           | 1000/9000                    | Drug-containing fodder   | SD rat, male and female                      | -                 |                | [46] |
|                           | 6000/6000                    | Drug-containing fodder   | Guinea pig                                  | 60                | Yes            | [51] |
|                           | 3000/3000                    | Drug-containing fodder   | Guinea pig                                  | 60                |                |      |
|                           | 12000/12000                  | Drug-containing fodder   | Guinea pig                                  | 60                |                |      |
|                           | 24000/24000                  | Drug-containing fodder   | Guinea pig                                  | 60                |                |      |
|                           | 1160/1160                    | Drug-containing fodder   | Guinea pig, male and female                 | 56                |                | [40] |
|                           | 1160/1160                    | Drug-containing fodder   | Guinea pig, male and female                 | 28                |                |      |
|                           | 2000/2000                    | Drug-containing fodder   | Guinea pig                                  | 30                |                | [40] |
|                           | 4000/4000                    | Drug-containing fodder   | Guinea pig                                  | 60                |                |      |
|                           | 2000/2000                    | Drug-containing fodder   | Guinea pig                                  | 60                |                |      |
| Emodin                    | 100/6400                     | Drug-containing fodder   | KM mouse, male                               | 82                | No             | [47] |
| Rhein                     | 240/320                      | Gavage                   | Wistar rat, male                            | 115               |                | [48,49] |
|                           | 240/320                      | Gavage                   | SD rat, male and female                      | 110               |                | [27,28,31] |
|                           | 240/320                      | Gavage                   | Wistar rat, male                            | 114               |                | [27] |
| Total anthraquinone in rhubarb | 500/4500                    | Gavage                   | SD rat, male                                | 92                |                | [53] |
| Senna                     | 460/460                      | Drug-containing fodder   | Guinea pig, male and female                 | 28                | Yes            | [40] |
|                           | 460/460                      | Drug-containing fodder   | Guinea pig, male and female                 | 56                |                |      |
| Phenolphthalein           | 100/4000                     | Drug-containing fodder   | Wistar rat, male and female                 | 30                | No             | [9]  |
|                           | 200/3400                     | Drug-containing fodder   | Wistar rat, male and female                 | -                 |                | [20] |
|                           | 200/3200                     | Drug-containing fodder   | Wistar rat, male and female                 | 90                |                | [39] |
|                           | 200/3600                     | Drug-containing fodder   | Wistar rat, male and female                 | -                 |                | [39] |
|                           | 200/4200                     | Gavage                   | SD rat, male and female                      | 28                | Yes            | [52] |
|                           | 15430/15430                  | Gavage                   | Guinea pig, male and female                 | 56                |                |      |
|                           | 15430/15430                  | Gavage                   | Guinea pig, male and female                 | 56                |                |      |

SD: Sprague-Dawley.
COMPARISON OF LAXATIVE AND ANIMAL SELECTION

Comparison of chemicals
AQs, including rhein, emodin, chrysophanol, aloe emodin, emodin methyl ether, aurantrio-obtusin, obtusin, obtusifolin, and physcion, among others, are components of many herbal medicines. These medicines include Cassiae semen (Juemingzi in Chinese medicine); Rhizoma et Radix Polygoni Cuspidatum (Huzhang in Chinese medicine); Radix et Rhiza Rhei (Dahuang in Chinese medicine); Radix Polygoni Multiflori (Heshouwu in Chinese medicine); Aloe (Luhui in Chinese medicine); and Senna leaf (Fanxiye in Chinese medicine). For thousands of years, they have all been used as traditional medicines to treat constipation in many East Asian countries, including China, Japan, and Korea.

In plants, AQs are predominantly glycosylated, and after oral administration, cannot be broken down by α-glucosidase in gastric acid or in the small intestine, because of the β-glycosidic bond between the sugar and the AQ ring. Thus, AQs go directly into the large intestine, where they are broken down by bacterial beta-glucosidases and reductases. AQ derivatives stimulate intestinal nerves, inhibit Na⁺-K⁺-ATP enzymes, increase retention of bowel fluid, induce peristalsis in the large intestine, reduce absorption of colonic fluid and Na⁺, and promote defecation.

AQ-related drugs, which are often used to establish cathartic colon models, include rhubarb, total AQ in rhubarb, rhein, and emodin, among others. Radix et Rhiza Rhei (rhubarb) is the most common drug used to establish cathartic colon animal models because of its low cost and availability. Total AQ in rhubarb is an AQ extract from rhubarb. Rhein is a lipophilic AQ, which has no cathartic effect. However, its metabolite, anthrone rhein, which is formed by the action of intestinal microorganisms, has cathartic activity. Emodin is an AQ derivative that has been isolated mainly from the rhizome of rhubarb in Polygonaceae. Many experiments have proved that emodin can significantly increase movement of intestinal smooth muscle and promote secretions from the intestinal epithelium. Therefore, emodin has been used as a laxative for many years.

Although rhubarb has been widely used to induce cathartic colon animal models in many studies, its composition is complex, its laxative effects are unstable, and it can be easily affected by its source, variety, processing, and storage methods. In addition, the long-term use of rhubarb may affect other physiological systems, and thereby affect the development of cathartic colon. Pharmacological studies have shown that rhubarb has both laxative and anti-diarrheal components. When rhubarb was soaked or decocted for a short time, the dissolution rates of AQ glycosides and other diarrheal components can be high. Nevertheless, the dissolution rate of tannin and other anti-diarrheal components may be high. Therefore, when rhubarb is used to induce cathartic colon animal models, the effects of decoction time on the bioactivity of rhubarb should be considered.

Rhein is a monomer with stable pharmacodynamics. Its quality remains stable and its concentration is easy to control.

The establishment of cathartic colon animal models by emodin and total AQ in rhubarb is rare, and needs further verification. Interestingly, the intestinal wall reportedly becomes thinner, telescopic function is poorer, and the time required for free stretching is prolonged in the cathartic colon model induced by total AQ in rhubarb. This is consistent with the findings of Smith in patients with cathartic colon.

In addition, diphenylmethane drugs and their derivatives, including phenolphthalein, bisacodyl, and sodium picosulfate, among others, are also commonly used to establish models of cathartic colon. Among these agents, phenolphthalein is the most common, even though it is almost insoluble in water. After oral administration, the soluble sodium salt is produced in the alkaline environment of the intestinal tract, which stimulates the intestinal plexus and directly affects the intestinal smooth muscle to increase intestinal peristalsis. Phenolphthalein can also inhibit intestinal absorption of water and electrolytes to cause defecation. The phenolphthalein-induced model has good reproducibility, and the dosage is easy to control. However, long-term use can easily lead to water and electrolyte disorders, hypoimmunity, and death in animals.

Feeding animals drug-containing diets ensures that they can freely obtain sufficient feed under conditions with limited human interference; however, it is difficult to strictly control the drug dosage administered to each animal. In contrast, intragastric administration can facilitate stricter control of the dosage and standardize the model, but also increase the influence of external factors. In addition, the method of administration may be affected by the solubility of the drug.
phenolphthalein is insoluble in water, but some researchers have used a phenolphthalein solution to induce a model of cathartic colon. This may have affected the effectiveness of the model. Furthermore, in many studies, the final doses of drugs are much higher than the typical clinical doses, which needs to be acknowledged.

**Animals selection**

The animals used to establish the cathartic colon model in most studies include rats, mice, and guinea pigs, among others. Rats are the first choice to establish this model. The anatomical and physiological characteristics of the rat are similar to those of humans, and it shows good adaptability to its environment, with low feeding costs. Wistar and Sprague-Dawley rats, 6-8 wk old, or 180-320 g in weight, male or female, are often used because they typically do not die easily, and yield high success rates. Mice, like rats, can be easily obtained and fed. However, compared with rats, only a few studies on cathartic colon models have used mice. Most pathological changes in cathartic colon (except melanosis coli) can be reproduced in the rat or mouse.

Guinea pigs are a little more expensive and have greater feeding requirements than rats and mice. However, melanosis coli can be easily induced in guinea pigs. This may be related to the fact that neither humans nor guinea pigs could synthesize vitamin C on their own\[24\]. Most studies theorize that melanosis coli is caused by damage to the intestinal mucosa after the long-term administration of laxatives, which may lead to apoptosis of colonic epithelial cells and the formation of apoptotic bodies. Apoptotic bodies can be phagocytized by mononuclear macrophages. Under the action of lysosomes, apoptotic bodies become decomposed and produce lipofuscin, which accumulates in the lamina propria to produce melanosis coli\[25\]. Interestingly, studies have shown that vitamin C protects intestinal epithelial cells from oxidant-induced apoptosis\[26\]. The mechanism by which vitamin C works in response to laxative-induced melanosis coli is unclear, and warrants further investigation.

**MODEL VERIFICATION**

The validity of the cathartic colon animal model has often been verified by examining the general physiological status, fecal water content, and intestinal transport functions in animals.

**Evaluation of general physiological condition**

Based on the changes in food intake, water intake, defecation frequency, stool characteristics, body weight, and hair color, disorders in animals may be evaluated\[21\].

**Measurement of fecal moisture content**

Low water content in feces is an indicator of constipation, and can be assessed to determine the severity of constipation in animals. The specific methods entail the collection of two to four fresh fecal pellets, and drying of those pellets in an oven at 150 °C for 15 min. To determine the moisture content of feces, the dry-to-wet ratio is calculated using the following formula: Dry fecal particle mass/fresh fecal particle mass × 100%\[27\].

**Determination of intestinal motility**

Slowing down of intestinal motility is one of the important clinical signs of cathartic colon. This can be determined by observing the first black stool of animals or calculating the propulsion rate of carbon powder.

**Observing expulsion time of the first black fecal pellet:** After being fasted for 24 h with free access to water, rats were given 2-3 mL 100 mL/L active carbon suspension by oral administration. The duration from the completion of gastric administration to the expulsion of the first black stool was recorded, to determine whether intestinal motility had slowed down\[28\].

**Calculation of the propulsion rate of carbon powder in the intestines:** Rats were sacrificed 30 to 40 min after gavage of active carbon, and the abdominal cavity was opened. The whole small intestine from the pylorus to the end of the rectum was removed. The entire length of the small intestine and the propulsion distance of the active carbon were measured under no strain. The propulsion rate of active carbon was calculated as distance travelled by the carbon from the pylorus/total length of intestine × 100%\[9,18,21\].
APPLICATION OF MODELS

Animal models are often used to investigate the pathogenic mechanisms of cathartic colon by observing histopathological changes in the intestines, and measuring the expression of related mRNAs and proteins by PCR and Western blot analysis.

Histopathological examination of the colon
A segment of colonic tissue was fixed in 40 g/L polyformaldehyde, dehydrated with gradient alcohol, embedded with paraffin, and stained with hematoxylin and eosin or undergoes intermuscular plexus argyrophil staining or melanin staining. Inflammatory cell infiltration changes in intermuscular neurons, epithelial cell exfoliation, weakening or disappearance of argyrophilia of the myenteric plexus, and brown pigment granules have all been observed in the colon of cathartic colon animal models.

Expression of related factors in intestinal tissue
The mRNA and protein expression of opioid receptors and opioid receptor signal-regulating proteins (RGS4 and β-arrestin2) was increased in animals with cathartic colon. However, the expression of the mRNA and protein of the tyrosine kinase receptor (c-Kit) and its ligand stem cell factor (SCF) was significantly decreased. The increased expression of TNF-α have also been reported. Moreover, abnormal P75 (a nerve growth factor receptor) levels in the colon have been detected through immunohistochemical methods.

EXPECTATIONS

Overall, there are presently an insufficient number of animal models of cathartic colon available. Particularly, there are few models with melanosis coli except cathartic colon guinea pigs. We cannot yet determine whether or not melanosis coli occurs in rat and mouse models, owing to the short duration in establishing the model. The dynamic changes in rats or mice with cathartic colon should be observed over a longer period.

Second, standard operating procedures for cathartic colon modeling should be established. The process of cathartic colon modeling is closely related to the patient’s constitution, age, and the type, dose, and time of laxative administration. However, the age, strain, and the type, dose, and time of laxative administration may vary in the models established in different studies. Furthermore, it is difficult to set a time point at which to modify the dose of the laxative, based on the presence or absence of dilute feces, as described in existing studies. Further studies are required to improve the reproducibility of cathartic colon animal models.

Third, the pathological processes of the presented animal models are not completely consistent with those of clinical patients. For example, most patients abuse laxatives because of constipation, while almost all animals are healthy before administration of the laxative. Novel methods are needed to guide the establishment of animal models or modification of existing models.

Moreover, some obese patients abused laxatives to lose weight, which induced cathartic colon. Some studies have shown that low body mass index, lower fiber intake, and less physical activity all increase the likelihood of chronic constipation. While some studies have found that fiber is not beneficial to constipation. In addition, the prevalence of chronic constipation increases with age, and is higher in women than in men. Anxiety, depression, and other psychological factors are also risk factors for constipation. These indicated that age, gender, body mass index, physical activity, mood, and abnormal fiber intake also influence the outcomes of cathartic colon animal modeling.

CONCLUSION

Although the existing animal models can be used as powerful tools to study cathartic colon to some extent, there are still challenges that must be acknowledged. Therefore, we still need to explore and establish more standardized modeling programs, which could more effectively reproduce animal models that are similar to the physiological conditions of patients with cathartic colon.
REFERENCES

1. Ho M, Zhang B, Ding S, Ding Y, Chen Y. Evaluation of Therapeutic Effect of Jichuanjian on Cathartic Colon. Iran J Public Health 2016; 45: 542-543 [PMID: 27252927]

2. Chen MH, Hou XH. Common views of Chinese experts on chronic constipation (2019, Guangzhou). Zhonghua Xuehuan Za Zhi 2019: 577-598 [DOI: 10.3760/cma.j.issn.0254-1432.2019.09.001]

3. El-Salhy M. Chronic idiopathic slow transit constipation: pathophysiology and management. Color Res 2005; 5: 288-296 [PMID: 12814404 DOI: 10.1006/jcre.2003.00498.x]

4. Wang YB, Ling J, Zhang WZ, Li G, Qiu W, Zheng JJ, Zhao XH. Effect of bisacodyl on rats with slow transit constipation. Braz J Med Biol Res 2018; 51: e7372 [PMID: 29344610 DOI: 10.1590/1414-431x.20187372]

5. Xing JH, Soffer EE. Adverse effects of laxatives. Dis Colon Rectum 2001; 44: 1201-1209 [PMID: 11535863 DOI: 10.1007/BF02234645]

6. Heilbrun N. Roentgen evidence suggesting enterocolitis associated with prolonged cathartic abuse. Radiology 1943: 1-9 [DOI: 10.1148/41.5.486]

7. Smith B. Pathology of cathartic colon. Proc R Soc Med 1972; 65: 288 [PMID: 5083323]

8. Clain J, Novis BH, Bank S, Kahn LB, Marks IN. Cathartic colon with unusual histological features. S Afr Med J 1974; 48: 216-218 [PMID: 4814497]

9. Zheng LY, Gao F, Tong WD, Zhang SB, Huang XK. Establishment of a cathartic colon rat model. Shiji Huren Xiaohua Zazhi 1998; 6: 864-866 [DOI: 10.19613/j.cnki.1671-3141.2019.05.142]

10. Hai DH. Research progress of rhubarb. Shiji Zixiu Ye Xuei Xiei Wenzhai 2019; 19: 196-197 [DOI: 10.19613/j.cnki.1671-3141.2019.05.142]

11. Yang J, Zha A, Xiao S, Zhang T, Wang L, Wang Q, Han L. Anthraquinones in the aqueous extract of Cassiae semen cause liver injury in rats through lipid metabolism disorder. Phytomedicine 2019; 64: 153059 [PMID: 31401496 DOI: 10.1016/j.phymed.2019.153059]

12. Yan J, Wang Y, Wu H, Sun Z, Tan S, Wang W, Gong L, Xie X, Li S. Development of a Method for Simultaneous Determination of Two Stilbenes and Four Anthraquinones from Polygonum Cuspidatum by RP-HPLC. JAOAC Int 2018; 102: 69-74 [PMID: 30005720 DOI: 10.5740/jaoacint.18-0097]

13. Liu Z, Lan Y, Li L, Liang Z, Deng Y, Fang R, Meng Q. Effect of emodin on chondrocyte viability in an in vitro model of osteoarthritis. Exp Ther Med 2018; 16: 5384-5389 [PMID: 30542499 DOI: 10.3892/etm.2018.6877]

14. Fan Y, Niu Z, Xu C, Yang L, Yang T. Proctic Ionic Liquids as Efficient Solvents in Microwave-Assisted Extraction of Rhein and Emodin from Rheum palmatum L. Molecules 2019; 24: 2770 [PMID: 31366111 DOI: 10.3390/molecules24152770]

15. Lin L, Ni B, Lin H, Zhang M, Li X, Yin X, Qu C, Ni J. Traditional usages, botany, phytochemistry, pharmacology and toxicology of Polygonum multiflorum Thunb.: a review. J Ethnopharmacol 2015; 159: 158-183 [PMID: 25449462 DOI: 10.1016/j.jep.2014.11.009]

16. Lombardi N, Bettoli A, Crescioli G, Maggini V, Gallo E, Sivelli F, Sofi F, Gensini GF, Vannacci A, Firenzuoli F. Association between anthraquinone laxatives and colorectal cancer: a protocol for a systematic review and meta-analysis. Syst Rev 2020; 9: 19 [PMID: 31980030 DOI: 10.1186/s13643-020-1280-5]

17. Malik EM, Müller CE. Anthraquinones As Pharmacological Tools and Drugs. Med Res Rev 2016; 36: 705-748 [PMID: 27111661 DOI: 10.1002/med.21391]

18. Bao JQ, Li F, Zhang WS, Han H, Wang X, Li GH, Wang CH, Li JC. Mechanism of Zeng Ye Decoction on treating rat model of cathartic colon. Zhongguo Zhongxiyijiehe Xiaohua Zazhi 2007; 15: 354-357 [DOI: 10.3969/j.issn.1671-038X.2007.06.002]

19. Zhou YY, Xia W, Yue W, Peng C, Rahman K, Zhang H. Rhein: A Review of Pharmacological Activities. Evid Based Complement Alternat Med 2015; 2015: 578107 [PMID: 26185519 DOI: 10.11540/578107]

20. Liu H, Gao Y. Research progress in molecular mechanism of the pharmacological actions of emodin. Zhongguo Yaoxue Tongbao 2009; 25: 1552-1555 [DOI: 10.3321/j.issn.1001-1978.2009.12.004]

21. Liu X, Wang WG, Ci MM. Comparison of rat models of cathartic colon established with rhein and rhubarb. Shiji Huren Xiaohua Za Zhi 2014; 22: 1262-1265 [DOI: 10.11569/wcjd.v22.i9.1262]

22. Fu YD, Zhang J, Liu Y, Li L, Xiao YQ. Analysis on bidirectional regulation of purging and astrigency about raw and steamed Products of rhei radix et rhizoma and their active components. Zhongguo Shiyian Fangxiu Za Zhi 2019; 25: 127-132 [DOI: 10.13422/j.cnki.sfjx.2019.0406]

23. Liang B, Zou J, Su J. What makes the phenolphthalein still be a safe drug for patients in China? Pharmacoeconomics Drug Saf 2015; 24: 555-557 [PMID: 25906829 DOI: 10.1002/pds.3777]

24. Lachapelle MY, Drouin G. Inactivation dates of the human and guinea pig vitamin C genes. Genetica 2011; 139: 199-207 [PMID: 21140195 DOI: 10.1007/s10709-010-9537-x]

25. Walker NJ, Bennett RE, Axelsen RA. Melanosis coli. A consequence of anthraquinone-induced apoptosis of colonic epithelial cells. Am J Pathol 1988; 131: 465-476 [PMID: 3381879]

26. Miller MJ, Angeles FM, Reuter BK, Bobrowski P, Sandoval M. Dietary antioxidants protect gut epithelial cells from oxidant-induced apoptosis. BMC Complement Altern Med 2001; 1: 11 [PMID: 11749672 DOI: 10.1186/1472-6882-1-11]

27. Huo MD, Zhang B, Chen YG. Therapeutic Effect of Jichuan Decoction on Rats With Cathartic Colon and Its Mechanism. Zhongguo Quanke Yexue 2016; 19: 1598-1601 [DOI: 10.3969/j.issn.1007-9572.2016.13.028]
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28 Huo MD, Ding SQ, Ding YJ, Jiang B, Zhang B. Role of SCF/c-Kit signaling pathway in the pathogenesis of cathartic colon. Shijie Huaren Xiaohua Zazhi 2013; 21: 809-813 [DOI: 10.11569/wcjdc.v21.i9.809]

29 Wu J, Liu B, Tong W, Zhang A, Li F, Lin J, Wang LJ. Opioid receptors and associated regulator of G protein signaling are involved in the cathartic colon of rats. Exp Ther Med 2015; 9: 1229-1234 [PMID: 25780414 DOI: 10.3989/etm.2015.203] [DOI: 10.3989/etm.2015.203]

30 Yang YQ, Wu ZY, Ma ZH, Chen JY. Evaluation of Intestinal Motility in Murine Melanosis Coli Caused by Rhubarb. Zhejiang Zhongyiijiehe Zazhi 2014; 24: 656, 678-679 [DOI: 10.3969/j.issn.1005-4561.2014.08.008]

31 Chen JY, Pan F, Zhang T, Xia J, Li YJ. Experimental study on the molecular mechanism of anthraquinone cathartics in inducing melanosis coli. Chin J Integ Med 2011; 17: 525-530 [PMID: 21725878 DOI: 10.1007/s11655-011-0786-2]

32 Fan YH, Lu B, Wang M, Ni GB, Chen MT, Xu Y. Expression and significance of nerve growth factor receptor p75 in rats' cathartic colonic wall. Chin J Dig Dis 2006; 7: 225-229 [PMID: 17054585 DOI: 10.1111/j.1443-9573.2006.00274.x]

33 Zhang B, Ding YJ. Establishment of rat model of cathartic colon by Rhein. Shizhen Guoyiguoyao 2012; 23: 1815-1816 [DOI: 10.3969/j.issn.1008-0805.2012.07.104]

34 Dukas L, Willett WC, Giovannucci EL. Association between physical activity, fiber intake, and other lifestyle variables and constipation in a study of women. Am J Gastroenterol 2003; 98: 1790-1796 [DOI: 10.1016/s0002-9270(03)00442-8]

35 Quah HM, Ooi BS, Seow-Choen F, Sng KK, Ho KS. Prospective randomized crossover trial comparing fibre with lactulose in the treatment of idiopathic chronic constipation. Tech Coloproctol 2006; 10: 111-114 [PMID: 16773290 DOI: 10.1007/s10155-006-0262-5]

36 Tan KY, Seow-Choen F. Fiber and colorectal diseases: separating fact from fiction. World J Gastroenterol 2007; 13: 4161-4167 [PMID: 1796243 DOI: 10.3748/wjg.v13.i13.4161]

37 Ho KS, Tan CY, Mohd Daud MA, Seow-Choen F. Stopping or reducing dietary fiber intake reduces constipation and its associated symptoms. World J Gastroenterol 2012; 18: 4593-4596 [PMID: 22969234 DOI: 10.3748/wjg.v18.i33.4593]

38 Cheng C, Chan AO, Hui WM, Lam SK. Coping strategies, illness perception, anxiety and depression of patients with idiopathic constipation: a population-based study. Aliment Pharmacol Ther 2003; 18: 319-326 [PMID: 12895216 DOI: 10.1046/j.1365-2036.2003.01663.x]

39 Liu BH, Mo P, Zhang SB. Effects of mu and kappa opioid receptor agonists and antagonists on contraction of isolated colon strips of rats with cathartic colon. World J Gastroenterol 2004; 10: 1672-1674 [PMID: 15162549 DOI: 10.3748/wjg.v10.i11.1672]

40 Tong WD, Zhang SB, BH Liu, Zhang LY, Huang XK, Gao F. Effect of rhubarb on colonic motility and enteric nervous system in rats. Shijie Huaren Xiaohua Zazhi 2003; 11: 665-667 [DOI: 10.3969/j.issn.1009-3079.2003.05.050]

41 Li HY, Yan X, Xue QL, Zhou YN, Gao Y, Wang R, Liu YM, Ran JT. Effects of nociceptin/orphanin FQ on rats with cathartic colon. World J Gastroenterol 2007; 13: 141-145 [PMID: 17206761 DOI: 10.3748/wjg.v13.i11.141]

42 Yan X, Wang JY, Liu YM, Wang J. Effect of endomorphin on colonic electromyography activity in endomorphin cathartic colon rats. Zhonghua Laojun Yaxue Zazhi 2006; 25: 298-300 [DOI: 10.3760/j.issn.0254-9026.2006.04.020]

43 Wang SY, Liu YP, Fan YH, Zhang L, Cai LJ, Lv B. Mechanism of aqueous fructus aurantii immaturus extracts in neuroplexus of cathartic colons. World J Gastroenterol 2015; 21: 9358-9366 [PMID: 26309361 DOI: 10.3748/wjg.v21.i31.9358]

44 Fang H, Li QL, Wang C, Zhang B, Liao XJ. Study on Intervention Effect of Simo Decoction on Cathartic Colon Rats. Zhonggua Zhongxiyiyao Xuekan 2014; 32: 888-890 [DOI: 10.13193/j.issn.1673-7717.2014.04.062]

45 Yu Q, Liu W, Jiang J, Liu RH. Melanosis of colon induced by different laxatives in guinea pigs: an experimental study. Beijingzhongyiyuodaxue Xuebao 2018; 41: 53-59 [DOI: 10.3969/j.issn.1006-2157.2018.01.009]

46 Zhao P, Luo JY, Dong L, Guan HT, Guo XD. Establishment of rhubarb-induced melanosis coli model in guinea pig. Zhongyiyiijiehe Xiaohua Zazhi 2006; 14: 308-311 [DOI: 10.3748/wjg.v14.i11.308] [PMID: 1671-038X.2006.05.009]

47 Huang W, Tang LJ, Zhang GH, Wang PH, Li K, Li W, Gu R, Zhang L. Changes of Amount of Intestinal Cells of Cajal and Expression of SCF/c-Kit in The Process of Cathartic Colon Induced by Emodin in Mice. Zhongguo Puwai Jihuaeilinchuang Zazhi 2016; 23: 406-410 [DOI: 10.7507/1007-9424.20160109]

48 Ci MM, Wang WG, Liu X, Zhang JH. Effect of Atractylodes macrocephala Koidz and Rehmannia dride rhizome on gastrointestinal motility in rats with cathartic colon. Shijie Huaren Xiaohua Zazhi 2015; 23: 1621-1626 [DOI: 10.11569/wcjdc.v23.i10.1621]

49 Wang WG, Ci MM, Zhang JH, Liu X, Meng XY. Establishment of rat model of cathartic colon and expression changes of c-kit mRNA in gastrointestinal tissues. Shandong Yiya 2015; 55: 4-6 [DOI: 10.3969/j.issn.1002-266X.2015.27.002]

50 Tong WD, Zhang SB, Liu BH, Zhang LY, Huang XK. Effects of phenolphthalein on colonic motility and enteric nervous system in rats. Zhonghua Xiaohua Zazhi 2003; 23: 723-726 [DOI: 10.3760/j.issn.0254-1432.2003.12.005]
