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Research Article
Gastroprotective Effects of *Dracaena cochinchinensis* (Lour.) Against Aspirin-Induced Gastric Ulcers in Rats

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Abstract

Background and Objective: Dragon's blood (DB) is a red colored resin, extracted from *Dracaena cochinchinensis* (Lour.). It has terrific medicinal importance due to presence of many phenolic compounds. This study was designed to explore gastroprotective properties of DB in aspirin-induced gastric ulcers. **Materials and Methods:** In this study 48 Sprague Dawley (SD) rats were divided into six groups. Normal and negative groups received water, while the positive group received Omeprazole (20 mg kg^{-1}). Remaining low, middle and high dose groups received DB (400, 800 and 1200 mg kg^{-1}), respectively as pre-treatment. Exactly after 1 h of pre-treatment, aspirin (250 mg kg^{-1}) were administered orally to all the groups except normal group. All drugs were administered continuously for 14 days. On 15th day, rats were sacrificed and their stomachs were collected. pH, acidity of gastric content, ulcer index, Gastric wall mucus (GWM) and other biochemical parameters like Prostaglandin E2 (PGE2), superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase (CAT) Malondialdehyde (MDA) and protein concentration were evaluated. **Results:** The DB shown a dose-related (63.98-85.18%) protection while Omeprazole showed (81.37%) protection. The DB also increased the pH and decreased the acidity of gastric contents. Gastric levels of SOD, CAT, GSH-Px were significantly ($p<0.001$) increased while MDA level was decreased. Furthermore, DB also enhanced the PGE2 level and mucus production. **Conclusion:** From the results of study, it was concluded that DB had sufficient potential to halt gastric ulcers by increasing antioxidant status and PGE2 level to produce mucus.

Key words: Gastro-protection, *Dracaena cochinchinensis*, aspirin, gastric ulcers, rats and omeprazole

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Gastric ulcer is an alarming and most prevalent disease of the gastrointestinal tract (G.I.T), around 10% of world population is suffering from this disease[1,2]. It is caused due to increase in the noxious factors like hydrochloric acid, free radicals, pepsin, bile salts etc., or decrease in defensive factors like mucus, prostaglandins, bicarbonates and normal tissue microcirculation[3]. The main factors which can produce gastric ulcer includes alcohol consumption, psychological stress, cigarette smoking, bacterial infection, nutritional deficiencies and unremitting use of non-steroidal anti-inflammatory drugs (NSAIDs)[4].

Aspirin is commonly prescribed for its antipyretic, analgesic and anti-inflammatory effects. Low doses of aspirin are used as an anti-thrombotic agent to avoid the heart attack, additionally; it may protect some types of cancers. In spite of several benefits, aspirin is supposed to be a common cause of gastric ulcers. The mechanism by which aspirin causes gastric ulcer is yet to be explored[5]. However, it is found that aspirin suppresses synthesis of prostaglandin (PG) by inhibiting cyclooxygenase (COX) enzymes and as a result hinders the secretion of mucus and bicarbonates. Furthermore, aspirin increases reactive oxygen species (ROS)[6] and cause gastric tissue damage by inducing lipid peroxidation and inhibiting antioxidant enzymes.

Presently a large number of allopathic drugs are used to cure gastric ulcers, which includes H2 receptor antagonist (famotidine, ranitidine), proton pump inhibitors (esomeprazole, Omeprazole), gastric mucosal protecting drugs (sucralfate, bismuth) and antibiotics to eradicate *H. pylori* infection[7]. But these medicines are expensive along with some side effects[8]. Besides, these medicines do not always offer an effectual and permanent treatment for the ulcer. That is why treatment of gastric ulcers still remains the main problem; hence there is an essential need to screen and introduce new, safe, effective and economical gastro-protective agents.

Dragon's blood (DB) is a red coloured resin, extracted from *Dracaena cochinchinensis* (Lour.) S.C. Chen (Agavaceae). It is recently discovered native dracaena species which becomes the major source of DB in China[9]. The DB possesses great medicinal importance while majority of its biological effects are due to the presence of phenolic compounds[10]. Previous pharmacological studies have shown that it can work as anti-helicobacter pylori and anti-diarrheal[11,12]. Moreover, recent studies of author's school revealed that DB has anti-thrombotic, anti-radiation, anti-inflammatory and analgesic effects[13-15]. As DB is rich in phenolic compounds hence this may possess possible gastro-protective properties, which has not been reported until now. The main objective of this study was to explore gastro-protective effect of DB extract. Furthermore, according to author's knowledge, this was the first report to evaluate the gastro- protective potential of DB.

MATERIALS AND METHODS

Drugs and chemicals: The DB powder (No. 20061120) was supplied by BIT&GY Pharmaceutical R&D Co. Ltd (Beijing, china). Both Aspirin and Omeprazole were obtained from J &K scientific Ltd. (Beijing, china). Alcian Blue purchased from BBI Life Sciences Corporation (Shanghai, China). Prostaglandin E2 (PGE2) Elisa Kit Obtained from Beijing Freemore Bioscience, Co., Ltd. (Beijing, china). Coomassie brilliant blue, glutathione peroxidase (GSH-PX),catalase(CAT), superoxide dismutase (SOD) and Malondialdehyde (MDA) assay kits were purchased from Jiancheng Institute of Bioengineering (Nanjing, China). All other reagents were of commercially available analytical grade.

Animals: Male SD rats weighing 220-250 g were provided by Military Medical Sciences Experimental Animal Co., Ltd. (Beijing, China). The rats were housed in an air-conditioned room maintained at a specific temperature of 22-25°C, humidity of 60-70% and at an alternating cycle of 12 h light plus 12 h dark. Animals were provided with standard class food pellets and water and they were cared according to guidelines of National Institute of Health (NIH)[16]. Animal ethics approval was obtained from Animal Ethics Committee, of Beijing Institute of Technology (BIT) having reference No: SYXK (Jing) 2012-0035.

Preparation of drugs: The DB extract was prepared in same way with small modification as described in the previous study[14]. In which crude DB was weighed and completely dissolved in 85% ethanol at room temperature. Then distilled water was added to dilute the solution up to 50% ethanol. The resultant solution kept at room temperature for 24 h and filtered. The residue was again dissolved in 85% ethanol and the same process was repeated. Both the first and second filtrates were pooled, evaporated by rotary evaporator at 40°C. The main phenolic compounds present in DB extract were shown in Fig. 1. Above prepared DB extract were used to check the gastroprotective activity.

All the drugs were freshly prepared on daily basis just before use. The aqueous suspensions of DB were prepared by

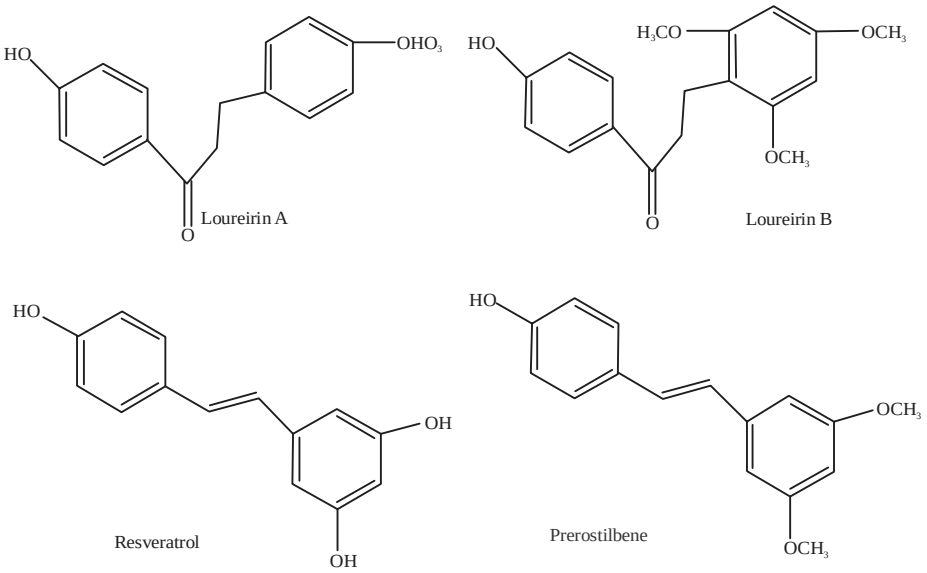

Fig. 1: Main phenolic compounds present in Dragon's blood

using 0.5% sodium carboxymethyl cellulose (Sod. CMC) as a suspending agent, moreover, drugs were administered intra-gastrically to rats at appropriate doses.

Experimental procedure: Before start of the experiment, animals were kept in a pre-experimental phase of one week to acclimatise the environment of the animal house. After that, they were divided randomly into 6 experimental groups. Water was given to normal and negative control groups. Whereas, the positive control group, received Omeprazole 20 mg kg^{-1}. Remaining low, middle and high dose groups received DB extract (400, 800 and 1200 mg kg^{-1}) respectively. Exactly after 1 h aspirin (250 mg kg^{-1}) was administered to all groups except normal control. Drugs were administered intragastrically once a day, continuously for 14 days. On 15th day, rats were sacrificed and their stomachs were collected for further analysis.

Assessment of pH, free and total acidity of gastric content: The gastric fluids were collected simply by squeezing the stomach, so that the gastric fluids oozed out through the esophageal junction. Subsequently collected gastric fluid were centrifuged at 3500 rpm (revolution per minute) for 15 min to remove the residual debris and to collect clear supernatant. Resultant clear supernatant was used to measure pH and acidity of gastric juice. Digital pH meter was used to measure pH of gastric contents and titration method of Srivastava *et al.*[17]. were used to measure free and total acidity of gastric contents.

Evaluation of gastric wall mucus (GWM): For assessment of GWM, followed the Method Corne *et al.*[18]. In this weighed glandular gastric segments were immediately added into 10 mL (0.1%) Alcian blue solution (containing buffered 0.16 M sucrose solution, having pH of (5.0) and kept for 2 h. Excessive dye was removed by rinsing with 0.25 M sucrose solution and 10 mL magnesium chloride (0.5 M) were used to extract alcian blue dye combined with mucus by a constant shaking of 1 min after every 30 min for 2 h. Afterwards, 0.4 mL of the extract was strongly shaken with 0.4 mL of ether and centrifuged at 3500 rpm for 10 min. The supernatants were collected and analyzed by spectrophotometer at a wavelength of 580 nm. The amount of mucus was quantified by comparing with the standard curve.

Estimation of gastric damage: For evaluation of mucosal lesions, stomachs were opened along with greater curvature and washed with cold physiological saline to remove gastric bubble and blood clots. The sum of length (mm) of the entire lesions for each stomach were calculated and used as ulcer index. Protection (%) was calculated by following equation[19]:

$$\text{Protection}(\%) = \frac{\text{UI control} - \text{UI treated}}{\text{UI control}} \times 100$$

Measurement of biochemical parameters: Gastric tissue previously stored at -80°C were weighed and homogenised in

(10% w/v) normal saline by a glass homogenizer in cold environment at 4°C to collect the clear supernatant. The clear supernatant was used to measure the biochemical parameters like GSH-PX, CAT, SOD, MDA, PGE2 and protein concentration. Above mentioned assays were completed by using commercially available assay kits according to instructions of the manufacturer.

Histological evaluation of gastric mucosa: Hematoxylin-eosin (H.E) staining were performed to evaluate the histology of gastric mucosa. In which gastric tissues were fixed by 0.01 M PBS (pH 7.4) containing 4% formalin, dehydrated by gradient alcohol and then fixed in paraffin. After placing 5 μm thick tissue sample on glass slides it was deparaffinized and stained with hematoxylin-eosin dyes. Olympus BX50 (Olympus, Japan) microscope were used to observe the prepared slides. Moreover the Images were captured by Cool SNAP CCD (Photometrics, USA).

Statistical analysis: All the results were reported as Mean±S.E.M. Statistical analysis was performed by using one way ANOVA, followed by Student's t-test for comparing two groups. $p<0.05$ was considered to be significant.

RESULTS

Assessment of gastric lesions and protection (%): Protective effect of DB was shown in Table 1. Results of this study revealed that the rats pretreated with Omeprazole and different doses of DB had significantly ($p<0.001$) reduced aspirin-induced gastric ulcers. Practically no ulcer was seen in the normal group whereas aspirin caused 51.20±1.63 mm^2 ulcers in negative group. In the positive group, the ulcer area was considerably reduced by omeprazole with an average of 9.54±0.60 mm^2 and provides 81.37% protection. Pretreatment with DB shown significant ($p<0.001$) protection when compared with negative group.

Effect of DB extract on GWM contents: In this study aspirin significantly ($p<0.001$) reduced GWM in negative group as compared to normal group. While pretreatment with different doses of DB significantly ($p<0.001$) increased the GWM when compared to negative group. Likewise, the animals pretreated with Omeprazole also increased gastric wall mucus content but at lower extent as compared to DB extract (Table 2).

Effect of DB on protein concentration: As shown in Table 2, protein concentration was decreased by aspirin in gastric tissues of the negative group as compared to the normal group, whereas protein concentration was considerably increased ($p<0.001$) in positive and experimental groups when compared to negative control group.

Effect of DB extract on ph and acidity of gastric juice: As depicted in Table 3, aspirin caused considerable decrease in pH of gastric fluids from 3.21±0.01-1.25±0.03. While treatment with standard drug omeprazole and test drug DB significantly ($p<0.001$) increased the pH of gastric

Table 1: Effects of DB extract on aspirin-induced ulcer in rats

Groups	Dose (mg kg^{-1})	Ulcer index (mm)	Protection (%)
Normal	0.5% Sod. CMC	00.00	100.00
Negative	250	51.20±1.63***	00.00***
Omeprazole	20	09.54±0.60###	81.37###
Low dose	400	18.44±1.07###	63.98###
Middle dose	800	11.70±1.22###	77.14###
High dose	1200	07.59±0.68###	85.18###

Results are expressed as Mean±SEM and analyzed by ANOVA followed by Student's two-tailed t-test, *p<0.05, **p<0.01, ***p<0.001, compared with the normal group, #p<0.05, ##p<0.01, ###p<0.001, compared with the aspirin group

Table 2: Effects of DB extract on GWM and protein contents

Groups	Dose (mg kg^{-1})	GWM (Mcg g^{-1} tissue)	Protein (Mg prot mL^{-1})
Normal	0.5% Sod. CMC	131.44±0.58	3.37±0.025
Negative	250	71.97±0.58***	2.63±0.06***
Omeprazole	20	119.08±0.42###	3.25±0.019###
Low dose	400	102.67±0.83###	3.07±0.04###
Middle dose	800	122.25±0.86###	3.16±0.019###
High dose	1200	143.71±1.32###	3.27±0.02###

Results are expressed as Mean±SEM and analyzed by ANOVA followed by Student's two-tailed t-test, *p<0.05, **p<0.01, ***p<0.001, compared with the normal group, #p<0.05, ##p<0.01, ###p<0.001, compared with the aspirin group

Table 3: Effects of DB on gastric contents of aspirin-induced ulcer in rats

Group	Dose (mg kg^{-1})	pH	Free acidity (mEq L^{-1})	Total acidity (mEq L^{-1})
Normal	0.5% Sod. CMC	3.13±0.01	63.71±0.42	108.04 ±0.71
Negative	250	1.25±0.03***	81.20±0.39***	146.50 ±0.79***
Omeprazole	20	3.21±0.01###	57.49±0.52###	103.83 ±0.55###
Low dose	400	2.31±0.02###	74.01±0.65###	122.67±0.50###
Middle dose	800	2.84±0.02###	69.41±0.49###	118.84±0.57###
High dose	1200	3.51±0.02###	64.63±0.34###	110.02 ±0.33###

Results are expressed as Mean±SEM and analyzed by ANOVA followed by student's two-tailed t-test, *p<0.05, **p<0.01, ***p<0.001, compared with the normal group, #p<0.05, ##p<0.01, ###p<0.001, compared with the aspirin group

Table 4: Effects of DB on SOD, CAT, GSH-Px and MDA in aspirin-induced ulcer in rats

Groups	Dose (mg kg^{-1})	SOD (units mg^{-1} prot.)	CAT (units mg^{-1} prot.)	GSH-Px (units mg^{-1} prot.)	MDA (nmole mg^{-1} prot.)
Normal	0.5% CMC	34.44±0.38	9.13±0.04	204.81±1.03	12.47±0.14
Negative	250	20.49±0.34***	4.51±0.03***	149.24±1.87***	16.99±0.13***
Omeprazole	20	33.48±0.41###	8.80±0.03###	197.02±0.93###	14.15±0.13###
Low dose	400	26.28±0.20###	7.30±0.25###	177.78±1.17###	15.67±0.16###
Middle dose	800	30.01±0.18###	8.48±0.04###	194.26±0.54###	13.36±0.11###
High dose	1200	33.41±0.17###	7.93±0.06###	203.38±0.97###	12.88±0.11###

Results are expressed as Mean±SEM and analyzed by ANOVA followed by student's two-tailed t-test, *p<0.05, **p<0.01, ***p<0.001, compared with the normal group, #p<0.05, ##p<0.01, ###p<0.001, compared with the aspirin group

juices. Furthermore; administration of both Omeprazole and DB caused a significant decrease (p<0.001) in the total and free acidity of gastric fluids.

Effect of DB on CAT, GSH-Px, SOD and MDA activity: In this study, it was observed that antioxidant activities in gastric tissue homogenates were different among the groups. Aspirin had significantly (p<0.001) reduced GSH-Px, SOD, CAT activities and enhanced MDA activity in gastric tissues of negative group as compared to normal group. Conversely, standard drug Omeprazole and test drug DB caused a significant increase (p<0.001) in GSH-Px, SOD, CAT and decrease in MDA level when compared to negative control group. The decrease in MDA activity by DB extract was in proportion to the increasing test doses as illustrated in Table 4.

Effect of DB on PGE2 level: As depicted in Fig. 2, that PGE2 level was reduced by aspirin in the negative group as compared to the normal group. But, both DB extract and Omeprazole significantly replenished the depressed PGE2. The increase in PGE2 content by DB extract was in proportion to the increasing test doses; because high dose of DB resulted significant augmentation in PGE2 contents.

Histological evaluation of gastric lesions: As illustrated in Fig. 3, no Pathological changes were found in the gastric mucosa of normal group animals (Fig. 3a) but large scale damage in glandular mucosa, hemorrhage and inflammatory

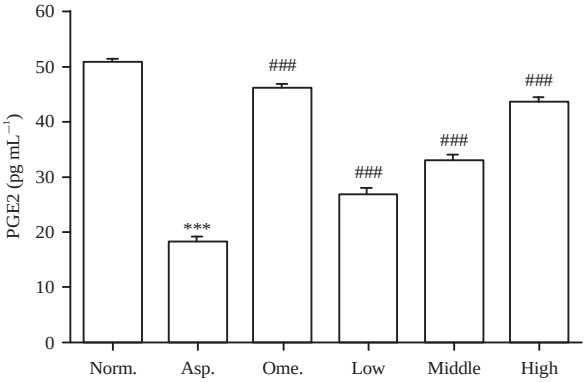

Fig. 2: Results are expressed as Mean±SEM
*p<0.05, **p<0.01, ***p<0.001, compared with the normal group, #p<0.05, ##p<0.01, ###p<0.001, compared with the aspirin group

cell infiltration around the necrotized area were observed in the negative group (Fig. 3b). While small scale necrosis was present in low dose group (Fig. 3d). Whereas pretreatment with both middle and high dose of DB (Fig. 3e-f) had provided significant (p< 0.001) protection of gastric tissues as compared to negative group and omeprazole group (Fig. 3c).

DISCUSSION

Chinese herbal drugs have great importance due to their therapeutic efficacy, safety, along with convenient applications. The DB a preeminent traditional Chinese drug due to its great medicinal benefits. The current study was conducted to observe the gastroprotective effects of different doses (400, 800 and 1200 mg kg^{-1}) of DB against aspirin-induced stomach ulcers in rats.

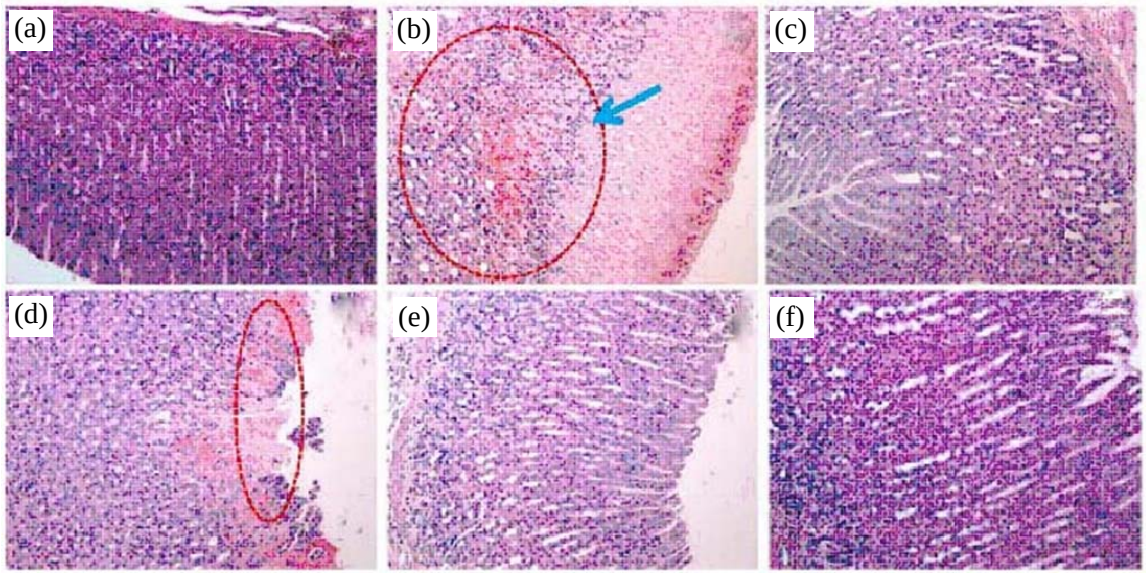

Fig. 3(a-f): Effect of DB extract on histological assessment in aspirin-induced stomach ulcer of rats (HE staining, magnification 100×) (a) Normal control group: Rats pretreated with water, (b) Negative control: indicates large scale necrosis (red encircled) and blue arrow indicates inflammatory cell infiltration in glandular stomach mucosa, (c) Positive control: Omeprazole (20 mg kg^{-1})+aspirin (d) Low dose: DB Extract (400 mg kg^{-1})+aspirin; indicate small scale necrosis (red encircled) in stomach mucosa, (e) Middle dose: DB Extract (800 g kg^{-1})+aspirin and (f) High dose: DB extract (1200 mg kg^{-1})+aspirin

Aspirin is powerful PGE2 biosynthesis inhibitor[20]. PGE2 in G.I.T is responsible for production of bicarbonates and mucus, which will protect ulcer by inhibiting acid secretions in the stomach[21]. Inhibition of prostaglandin synthesis by aspirin will decrease mucus production and cause gastric ulcers. In this study, PGE2 and gastric wall mucus contents were decreased by aspirin but improved by pretreatment with DB, these results of present study were parallel to some previous studies[22-24].

In addition, some previous studies proved, that aspirin will also generate ROS (reactive oxygen species), which cause stomach ulcers[25]. While enzymes like GSH-Px, SOD and CAT are responsible for composing an endogenous antioxidant system, which offers a defence against gastric damage by ROS.

According to a previous study NSAIDs will enhance the MDA and reduce the level of antioxidant enzyme in stomach[26]. Likewise, this study resulted that negative group treated with aspirin has increased the level of MDA and decreased the antioxidant enzymes in gastric tissues. While DB has increased the level of antioxidant enzymes and decreased the level of MDA in gastric tissues.

In addition, aspirin has a tendency to reduce the pH of gastric juices[27]. This study also revealed that pH of gastric juice was decreased in the aspirin-treated group but increased by pretreatment with DB.

Furthermore, no any toxicity and behavioral changes were observed during the provision of DB continuously for 14 days. Above results suggested that drug has excellent profile of safety and great potential to protect aspirin-induced stomach ulcers.

CONCLUSION

Results of this study undoubtedly demonstrate that DB possess excellent gastroprotective effects in aspirin-induced stomach ulcer. In this study, it is observed that DB has decreased the MDA and increased the pH, level of antioxidant enzymes, GWM and PGE2. The gastroprotective potential might be due to an enhancement of antioxidant status and increase in biosynthesis of PGE2. Therefore, results of this study indicates that DB could be the safe, new potential drug to protect stomach ulcers.

SIGNIFICANT STATEMENT

This study discovers the gastroprotective effect of Dracaena cochinchinensis (Dragon's blood) in aspirin-induced gastric ulcers that can be beneficial to decrease the risks of gastric ulcer caused by NSAIDs like aspirin. This study will help the researchers to find the prospective compounds responsible for gastroprotection that many researchers were not able to explore. Thus a new idea on combination of DB or its possible potential compounds and NSAIDs like aspirin may prevent the gastric ulceration the in patients on long-term therapy of NSAIDs.

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