Songklanakarin J. Sci. Technol.
40 (2), 258-263, Mar. - Apr. 2018

http://www.sjst.psu.ac.th

Original Article

Gastroprotective effects of methanolic extract of kratom leaves on gastric ulcer and reflux esophagitis in rats

Somsmorn Chittrakarn[1*], Nisaudah Radenahmad[2], Sujitra Kaewsara[3], Wandee Udomuksorn[1], Niwat Keawpradub[4], and Pimpimol Phukpattaranont[5]

[1] *Department of Pharmacology, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla, 90110 Thailand*

[2] *Department of Anatomy, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla, 90110 Thailand*

[3] *Department of Chemistry, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla, 90110 Thailand*

[4] *Department of Pharmacognosy and Pharmaceutical Botany, Faculty of Science, Prince of Songkla University, Hat Yai, Songkhla, 90110 Thailand*

[5] *Scientific Equipment Center, Prince of Songkla University, Hat Yai, Songkhla, 90110 Thailand*

Received: 6 June 2016; Revised: 27 September 2016; Accepted: 10 December 2016

Abstract

Kratom (*Mitragyna speciosa* (Korth.) Havil.) is a tropical tree indigenous to Thailand. In traditional medicine, it has been used to treat diarrhea, peptic ulcer, stomach ache or gastric upsets. In this study, the protective effects of a methanolic extract of kratom leaves on peptic ulcer models and reflux esophagitis in rats were studied. A methanolic extract of kratom leaves at a dose of 200 and 400 mg/kg were tested in rats on three induced peptic ulcer models and reflux esophagitis. The peptic ulcer models were induced by water immersion restraint (WIR) stress, alcohol treatment, and acetylsalicylic treatment. The methanolic extract of mitragynine from kratom leaves and ranitidine decreased the ulcer index significantly in the WIR stress model. Conclusion: Only 400 mg/kg of methanolic extract of kratom leaves and omeprazole decreased the ulcer index in the alcohol and acetylsalicylic acid induced ulcer models. No protective effect of kratom extract was found on the reflux esophagitis model.

Keywords: *Mitragyna speciosa* (Korth.) Havil., kratom, gastric ulcer, reflux esophagitis, mitragynine

1. Introduction

Kratom (*Mitragyna speciosa* (Korth.) Havil.) is a local tree in Southeast Asia such as Thailand and Malaysia. Native people use its leaves to help them do heavy work in the sun (Suwanlert, 1975) and it has also been a traditional medicine for hundreds of years.

The Thai government enacted the Narcotics Act B.E. 2522 (1979), placing kratom along with cannabis in the Category V of a five category classification of narcotics (Assanangkornchai & Sirivongs Na Ayudhya, 2005). The kratom tree is indigenous to the country and the native people

*Corresponding author
Email address: somsmorn.c@psu.ac.th

have used the leaves in the same way as the people in Peru and Bolivia have used coca leaves (*Erythroxylum coca*). Hence, kratom remains a popular drug in Thailand, especially in the southern regions. Thai natives chew kratom leaves to feel better and work harder. The regular users take 10-80 leaves per day. The occasional users take 1 to 20 leaves per day (Saingam *et al.,* 2013).

Mitragynine is the primary active indole alkaloid and the most important of over 25 alkaloids isolated from kratom leaves. Many alkaloids of this leaf tree have demonstrated psychoactive effects (Babua *et al.,* 2008). Kratom has been reported to be a central nervous system (CNS) stimulant and a CNS depressant. Kratom is also used to treat diarrhea (Chittrakarn *et al.,* 2008). It is also used to treat muscle ache and muscle strain because kratom can produce skeletal muscle relaxation (Chittrakarn *et al.,* 2010). Crude alkaloids of kratom leaves stimulate glucose transporter in muscle cells for the treatment of diabetes (Purintrapiban *et al.,* 2011). In folk medicine, it was reported to treat peptic ulcer, stomach ache or gastric upset. Therefore, it was of interest to study the *in vivo* protective effect of a crude methanolic extract of kratom leaves on a rat peptic ulcer model.

2. Materials and Methods

2.1 Plant material

Mature leaves of a kratom tree more than 5 years old were collected during the summer season (April) in Satun Province in the southern part of Thailand. This plant was identified by a taxonomist, from the Department of Biology, Faculty of Science, Prince of Songkla University. A specimen was deposited at the PSU Herbarium with the voucher number PSU 012821.

2.2 Preparation of the methanolic extract

Air-dried leaves were ground and macerated twice in absolute methanol for 7 days with stirring 3 times/day at room temperature. The extracts were combined, filtered, and then mixed and concentrated using a rotary evaporator (Buchi, B169 Vacuum-System, Switzerland). They were then freeze-dried (Corrosion Resistant Freezer Drier, FTS System, Inc., USA.). One hundred grams of fresh leaves of *Mitragyna speciosa* (Korth.) Havil. yielded 7.92 g of the methanolic extract. The methanolic extract of kratom leaves contained 1.56% w/w of mitragynine. This mitragynine extraction was approximately 98% pure as previously described (Janchawee *et al.,* 2007).

2.3 Chemicals

Acetylsalicylic acid, sucralfate, and omeprazole were obtained from Sigma-Aldrich and ranitidine was obtained from Millimed Co., Ltd. The solvent vehicle for dissolving the test materials was prepared by mixing propylene glycol, Tween 80, and distilled water (4:1:4). This mixture was diluted with distilled water to 1:10. The methanolic extract of kratom leaves was dissolved in 10 mL/kg of the solvent vehicle. The reagents used in this study were of analytical grade. Mitragynine was provided by Asist. Prof. Niwat Keawpradub.

2.4 Experimental animals

Adult male Wistar rats were provided by the Southern Laboratory Animal Facility, Prince of Songkla University. The rats weighed in the range of 200-250 g. Their home cages were controlled at a room temperature 25±2 ºC with a relative humidity of 50±5% and a 12-h light/12-h dark cycle. They were fed with animal food pellets and water *ad libitum*. The rats were fasted for 12 h before the experiments but were allowed drinking water *ad libitum*. The study protocol was approved by the Animal Ethical Committee, Prince of Songkla University with reference code 03/51.

2.5 Experimental models and treatments

The treatments were divided into 4 experimental models. There were 8 rats per group in each experimental model.

Model I was the water immersion restraint (WIR) stress. This model was divided into 5 groups. The rats received the vehicle, a methanol extract of kratom leaves at a dose of 200 and 400 mg/kg, mitragynine 2 mg/kg or ranitidine 50 mg/kg at 1 h before immersion in the water. They were tied to a plastic board and their entire bodies except for the heads were immersed vertically to the level of the xiphoid process in a water bath maintained at 19±1 °C for 6 h (Takagi & Okabe, 1968). The animals were not disturbed in their home cages that served as additional stress prevention. The rats were sacrificed after 6 h of water immersion.

Model II was the alcohol induced gastric ulcer. This model was divided into 4 groups composed of vehicle, kratom extract in the dose of 200 and 400 mg/kg, and omeprazole 20 mg/kg at 1 hour before receiving ethanol. Gastric ulcer was induced in rats by administering 2 mL of absolute ethanol. After 1 h of ethanol administration, the animals were sacrificed and the stomachs were removed.

Model III was acetylsalicylic acid induced gastric ulcers. This model was divided into 4 groups. The rat groups were administered the vehicle, kratom extract at a dose of 200 and 400 mg/kg, or 20 mg/kg of omeprazole 1 h before receiving acetylsalicylic acid. The rats received orally 300 mg/kg of acetylsalicylic acid to induce gastric ulcer. After 6 h of acetylsalicylic acid administration, the animals were sacrificed.

Model IV was the reflux esophagitis. Briefly, the rats were anesthetized with 75 mg/kg ketamine (i.p.). The abdomen was incised along the midline and then both the pyloric end of the stomach and limiting ridge (the transitional region between the fore stomach and corpus) were simultaneously ligated tightly, resulting in reflux of the gastric juice into the esophagus (Nakamura *et al.*, 1982). The test drugs were administered immediately after the ligation. These agents were vehicle, kratom extract at a dose of 200 and 400 mg/kg, or 500 mg/kg of sucralfate. Then the abdomen was sutured and they were allowed to recover from the anesthesia. The rats were then deprived of food and water. After 6 h of ligation the animals were sacrificed and the esophagus was removed and incised lengthwise.

2.6 Stomach removal

The rats were all sacrificed immediately by cervical dislocation at the end of their experimental models. Their stomachs were rapidly removed and incised along the greater curvature to observe the gastric lesions which appeared as hemorrhagic bands along the mucosal ridges of the stomach. The gastric contents were collected for gastric acid study. The stomach was rinsed gently with normal saline. Hemorrhagic lesions were observed with a microscope (DP11, Olympus SZX 12, Japan) and the area of the lesions was compared to the total area of the stomach and measured using the Image Pro Plus program. The ulcer index was calculated according to this equation: ulcer index = hemorrhagic lesion area (mm^2)/ total stomach area (mm^2) x 100.

2.7 Gastric acid study

The stomach was cut along the greater curvature and all gastric content was collected. It was centrifuged at 1000 rpm for 10 min. The 2-3 drops of Topfer's reagent were added in 1 mL of gastric juice and titrated with 0.01 N NaOH. Phenolphthalein was used as an indicator (Anoop & Jegadeesan, 2003).

2.8 Histological examination

The stomach tissues were cut off and rinsed with saline solution to remove blood and debris adhering to the tissues. The tissues were then fixed in 10% buffered formalin for 24 h and embedded in paraffin blocks. The tissues were sectioned at 5 µm thicknesses. Routine hematoxylin and eosin (H&E) staining was applied to all groups. Five criteria were set for histopathological evaluation: 1) changes in epithelial surface, e.g., epithelial surface was incomplete or lost its shape, 2) changes in glandular morphology, e.g., glands were destroyed or lost their shapes, 3) inflammatory cell infiltration (white blood cells, e.g., lymphocytes, neutrophils infiltrated into mucosa and/or submucosa layers), 4) vascularization in the mucosa including the lamina propria and submucosa (i.e. blood vessels infiltrated into the submucosa and mucosa areas), and 5) submucosal layer widening (i.e. submucosa width had widened or narrowed.).

2.9 Data and statistical analysis

Data are presented as mean±S.E.M. Statistical analysis was performed by analysis of variance, SPSS PC v.11.5 for windows followed by a Tukey comparison test for comparison of more than two groups. A value of $P<0.05$ was considered significant.

3. Results

3.1 Effect of a methanolic extract of kratom leaves on the rat gastric ulcer induced models

On macroscopic examination (Figure 1), the WIR stress model induced gastric ulcer significantly greater

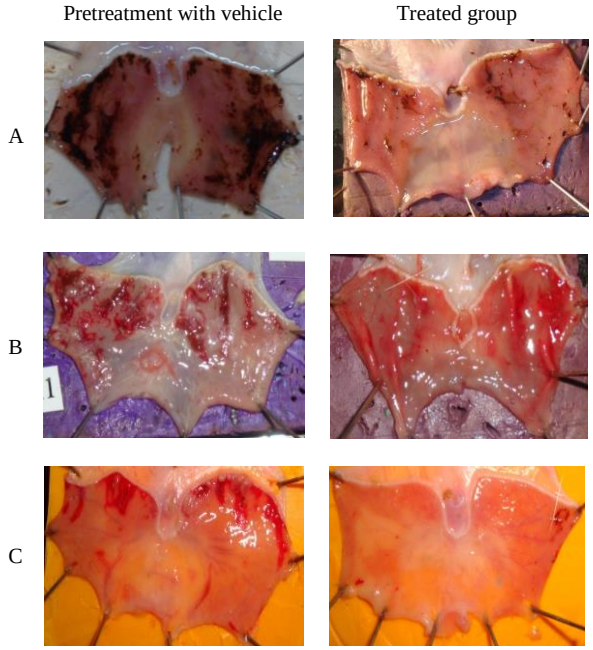

Figure 1. Macroscopic examination of the rat stomach induced ulcer using (A) the WIR stress model, (B) ethanol, and (C) acetylsalicylic acid compared with pretreatment with the vehicle (left hand column) and 400 mg/kg methanolic extract of kratom (right hand column).

($P<0.05$) than the alcohol induced ulcer model or the reflux esophagitis model (Table 1). The methanolic extract of kratom leaves at 200 and 400 mg/kg significantly decreased the ulcer indexes (7.21±3.40 and 2.79±0.76, respectively) in the WIR model compared to the vehicle ($P<0.05$). Ranitidine (50 mg/kg) and mitragynine (2 mg/kg) also decreased the ulcer indexes and showed a significant difference from the vehicle ($P<0.05$). In the alcohol induced ulcer model, only 20 mg/kg of omeprazole decreased the ulcer index to a significant difference from the vehicle ($P<0.05$). The methanolic extract of kratom leaves did not reduce the ulcer index. Only methanolic extract of kratom leaves at 400 mg/kg and omeprazole decreased the ulcer index to a significant difference from the vehicle ($P<0.05$) in the acetylsalicylic acid induced ulcer model. In the reflux esophagitis model, methanolic extract of kratom leaves at 400 mg/kg and sucralfate decreased the ulcer index to a significant difference from that of the vehicle ($P<0.05$) (Table 1).

3.2 Effect of methanolic extract of kratom leaves on the total acid and pH of gastric acid

The methanolic extract of kratom leaves at doses of 200 and 400 mg/kg seemed to decrease the total acid and increase the pH of the gastric acid contents. However, there were no statistically significant effects on the total acid and pH of the gastric acidity secretion in any of the induced ulcer models including the positive control (Table 2).

Table 1. Effect of a methanolic extract of kratom leaves (MS 200 and 400 mg/kg) and the standard drugs (mitragynine 2 mg/kg, ranitidine 50 mg/kg, omeprazole 20 mg/kg, sucralfate 500 mg/kg) on the rat induced ulcer models.

Agent	Ulcer index (mean±SEM, n=8)			
	WIR stress model	Alcohol induced ulcer model	Acetylsalicylic acid induced ulcer model	Reflux esophagitis model
Vehicle	26.96± 4.74	10.71±3.18[a]	17.04±4.05	12.45±2.83[a]
MS 200 mg/kg	7.21±3.40*	8.43±3.71	10.20±2.78	7.46±2.11
MS 400 mg/kg	2.79±0.76*	5.27±1.43	8.53±2.03*	3.02±1.74*
Mitragynine 2 mg/kg	5.90±2.49*	-	-	-
Ranitidine 50 mg/kg	3.86±0.82*	-	-	-
Omeprazole 20 mg/kg	-	2.45±1.60*	6.68±1.70*	-
Sucralfate 500 mg/kg	-	-	-	3.26±1.85*

Note: [a] Significantly different from the WIR stress induced ulcer model at $P<0.05$
* Significantly different from the vehicle group at $P<0.05$

Table 2. Effect of methanolic extract of kratom leaves (MS 200 and 400 mg/kg), mitragynine 2 mg/kg, ranitidine 50 mg/kg, omeprazole 20 mg/kg, and sucralfate 500 mg/kg on the total acid (mM) and pH of gastric secretion.

Agent	WIR stress model		Alcohol induced ulcer model		Acetylsalicylic acid induced ulcers model		Reflux esophagitis model	
	Total acid (mM)	pH	Total acid (mM)	pH	Total acid (mM)	pH	Total acid (mM)	pH
Vehicle	54.6±1.3	1.30±0.11	32.4±5.1	1.52±0.08	17.1±2.6	1.64±0.11	52.9±23.2	1.44±0.12
MS 200 mg/kg	32.6±1.1	2.14±0.13	46.5±15.1	1.54±0.17	16.0±2.7	1.82±0.07	47.4±13.3	1.54±0.19
MS 400 mg/kg	11.3±2.9	2.03±0.10	40.1±6.8	1.49±0.10	20.3±3.4	2.00±0.06	32.5±11.2	1.78±0.14
Mitragynine 2 mg/kg	8.7±3.6	2.22±0.16	-	-	-	-	-	-
Ranitidine 50 mg/kg	2.5±0.2	2.61±0.03	-	-	-	-	-	-
Omeprazole 20 mg/kg	-	-	21.0±2.6	1.70±0.05	21.4±6.2	2.01±0.08	-	-
Sucralfate 500 mg/kg	-	-	-	-	-	-	31.6±11.5	2.15±0.18

Note: The data are expressed as mean±SEM, n=8.

3.3 Effects of a methanolic extract of kratom leaves on the histopathological changes of the rat stomach

The histopathological assessment used five criteria as mentioned in the methods for histological examination (Figure 2). The criteria were the texture of the simple columnar epithelium cell, mucosal gland shape, white blood cell infiltration, submucosal width, and numbers of capillaries in the mucosa and also the submucosa layers. Methanolic extract of kratom leaves at 400 mg/kg dose developed more capillaries filled with red blood cells in the submucosa as well as the submucosal width compared to the kratom extract at 200 mg/kg in the WIR stress group and acetylsalicylic induced ulcer model. Inflammatory cell infiltration, mainly of neutrophils and lymphocytes, was also greater in the group pretreated with 400 mg/kg of kratom methanolic extract than in the 200 mg/kg of kratom methanolic extract and control groups. In addition, the epithelial surface was obviously damaged in the 400 mg/kg of kratom extract group compared with the 200 mg/kg of kratom methanolic extract group in the reflux esophagitis model. When compared with the other three models, the 400 mg/kg of kratom methanolic extract group was better than the 200 mg/kg of kratom methanolic extract group of the alcohol induced ulcer model using the five criteria. Methanolic extract of kratom leaves, mitragynine as well as ranitidine prevented the progression of gastric lesions in the WIR stress model. The epithelium showed less damage than the control. In the alcohol induced ulcer model, the epithelium of the gastric tissue was damaged and there were greater numbers of blood vessel infiltrations in the submucosal layer. The amounts of blood supply in the mucosa and submucosa of gastric tissues treated with kratom methanolic extract at 400 mg/kg dose were similar to those of the omeprazole group. In contrast, the numbers of capillaries in the mucosa and submucosa treated with 400 mg/kg kratom methanolic extract were less than the control group of the WIR stress model. After kratom methanolic extract treatment in the reflux esophagitis model, the tissues showed no significant changes.

These histopathological changes were not in accordance with gross morphology scored by the ulcer index. This was possibly due to the cellular changes that occurred prior to external morphology changes.

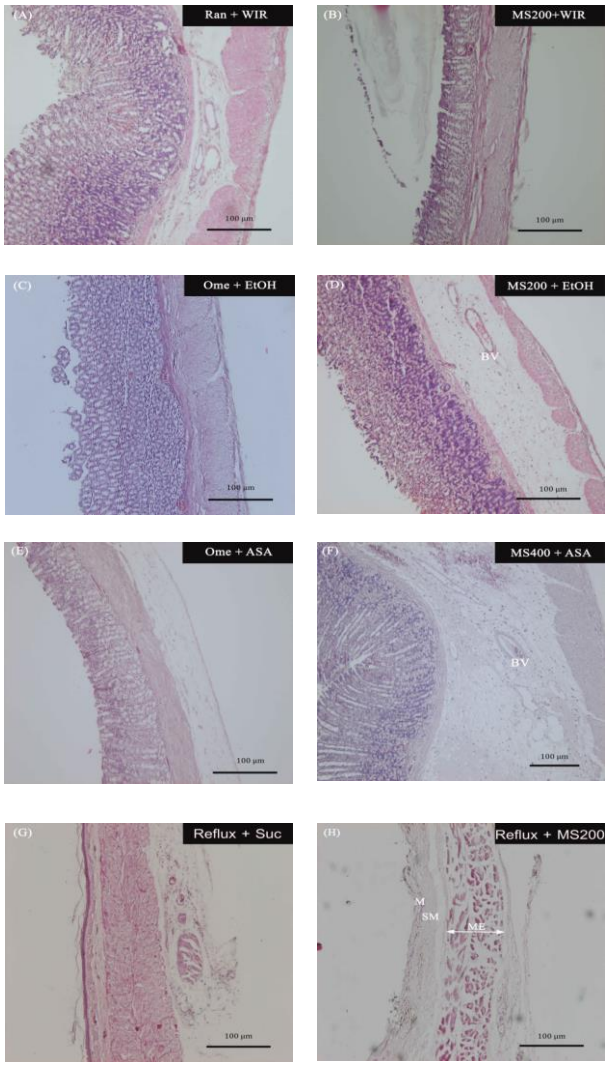

Figure 2. Microscopic views of the rat stomach (A-F) and esophagus (G-H) stained with hematoxylin and eosin (H&E).
(A) Gastric ulcer induced by immersing in cool water then receiving a standard drug, 50 mg/kg ranitidine (Ran+WIR) and (B) kratom extract 200 mg/kg (MS200+WIR)
(C) Gastric ulcer induced by ethanol then receiving standard drug, 20 mg/kg BW omeprazole (Ome+EtOH) and (D) kratom extract 200 mg/kg (MS200+EtOH)
(E) Gastric ulcer induced by acetylsalicylic acid (ASA) then receiving standard drug, 20 mg/kg omeprazole (Ome+ASA) and (F) kratom extract 400 mg/kg (MS400+ASA)
(G) Reflux esophagitis receiving standard drug, 500 mg/kg BW sucralfate (Reflux+Suc) and (H) kratom extract 200 mg/ kg (Reflux+MS200)
Note: M=mucosa; SM=submucosa; ME=muscularis externa; BV=blood vessel.

4. Discussion

The effect of a methanolic extract of kratom leaves on gastric ulcers and reflux esophagitis induced by four different models was investigated in this study. The four models were WIR stress, alcohol, and acetylsalicylic acid induced gastric ulcer and reflux esophagitis. The parameters investigated were the ulcer index, total acid (mM), pH of gastric content, and histopathological examination. Oral administration of methanolic extract of kratom leaves, ranitidine (histamine H2 antagonist), and mitragynine significantly inhibited gastric ulcer formation induced by the WIR stress. Mitragynine reduced gastric acid secretion via the opioid receptor in the CNS (Tsuchiya *et al.*, 2002). It was found that peripheral μ-opioid receptors involved the excitatory effects in the regulation of acid secretion while δ receptors produced mainly inhibitory effects (Intorre *et al.*, 1993). Thus, mitragynine may have a protective gastric ulcer effect via μ-opioid receptors.

The ulcer was a disruption of the mucosal integrity of the stomach and lower esophagus leading to a local defect. The ulcer broke on the mucosal surface with depth to the submucosa. According to the experimental models used in this study, in the alcohol induced gastric ulcer model, ethanol produced necrotic lesions by a direct necrotizing action which in turn reduced other defensive factors, the secretion of bicarbonate, and production of mucus (Marhuenda *et al.*, 1993). Ethanol induces the solubility of the gastric mucus constituents. Hydrochloric acid in the stomach aggravates ulcers triggered by ethanol, mainly due to the weakness of the protective mucosa of the stomach and exacerbation of gastric acid secretion and pepsin (Mizui & Doteuchi, 1983). Acetylsalicylic acid induced ulcer formation by depleting the cytoprotective prostaglandins. Prostaglandin E2 and prostaglandin I2 in the gastric and duodenal mucosa are responsible for mucus production and for maintaining the cellular integrity of the gastric mucosa (Bennett and Schultz, 1993). The WIR stress induced ulcers were caused by mucosal ischemia produced by the formation of a thromboxane A2-like substance and to the increased secretion of acid and a decreased mucus content (Kitagawa *et al.*, 1986). Gastric acid effectively leads to auto-digestion and breakdown of the gastric mucosa barrier. These may result in reduced gastric blood flow, thereby contributing to gastric ulcer formation (Zanatta, *et al.*, 2009).

The pure ethanol is lipid soluble and caused acute mucosal damage. The results found that kratom extract did not decrease the ulcer index in the alcohol induced ulcer model. Omeprazole was the only treatment that significantly decreased the ulcer index compared with the vehicle. However, the histological examination of the methanolic extract of kratom leaves was very similar to that of the omeprazole group. In the acetylsalicylic acid induced gastric ulcer model, the methanolic extract of kratom leaves decreased the ulcer index to the same extent as omeprazole. Omeprazole is a proton pump inhibitor and is the primary treatment when gastric hypersecretion is resistant to other therapies. Omeprazole most likely enhances ulcer healing due to its potent and persistent antisecretory effects (Sachs & Wallmark, 1989).

The methanolic extract of kratom leaves also decreased the ulcers induced by reflux esophagitis in the same way as sucralfate. Sucralfate reacts with hydrochloric acid in the stomach to form a cross-linked, viscous, paste-like material capable of acting as an acid buffer. It also attaches to proteins on the surface of ulcers to form stable, insoluble complexes to prevent further damage from acid, pepsin, and bile. Sucralfate also stimulates the increase of prostaglandin E_2, epidermal growth factors (EGF), and gastric mucus (Maton, 2003).

The methanolic extract of kratom leaves did not increase the gastric pH or decrease the total acid in the gastric content but it had a tendency to decrease the total acid in the gastric content. Gastric H^+, K^+-ATPase, exchanges luminal K^+ for cytoplasmic H^+ that is primarily responsible for gastric acid secretion. Kratom may not have any effects on the gastric acid pump.

5. Conclusions

The methanolic extract of kratom leaves and mitragynine had a protective effect in the WIR stress model. A high dose of the methanolic extract of kratom leaves decreased the ulcer index in the acetylsalicylic acid induced and reflux esophagitis models. However, it had no effect on the total gastric acid and pH of the gastric secretion. Histopathological analyses of gastric ulcers induced by various models revealed that pretreatment with methanolic extract of kratom leaves promoted moderate regeneration of ulcerous lesions (wound healing).

Acknowledgements

We gratefully acknowledge the financial support for this project from Prince of Songkla University (research grant no. SCI520033S).

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