Journal of
Clinical and Experimental Pharmacology

Ibrahim et al., Clin Exp Pharmacol 2012, S5
DOI: 10.4172/2161-1459.S5-004

Research Article Open Access

Leaves Extract of Muntingia Calabura Protects Against Gastric Ulcer Induced by Ethanol in Sprague-Dawley Rats

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Abstract

Aim: *Muntingia calabura* is a medicinal plant used popularly known in Malaysia against various diseases including peptic ulcer. This study was performed to evaluate the gastroprotective effect of ethanolic extracts of *Muntingia calabura* Leaf Extract (MCELE) against ethanol-induced gastric mucosal injury in experimental rats.

Methods: The rats were divided into four groups respectively pre-treated orally with Carboxymethyl Cellulose (CMC) solution (ulcer control groups), omeprazole 20 mg/kg (reference group), 250 and 500 mg/kg of MCELE (experimental groups) one hour before oral administration of absolute ethanol to generate gastric mucosal damage. After an additional hour, the rats were sacrificed and the ulcerated areas of the gastric walls were determined.

Results: The ulcer control group exhibited severe mucosal injury, whereas groups pre-treated with the MCELE exhibited significant protection of gastric mucosa. These findings were also confirmed by histology of the gastric wall. Significant increases in gastric mucus production and decrease in acidity of gastric content were observed in the treated groups with MCELE compare to ulcer control group.

Conclusions: The treatment with MCLELE prior to absolute alcohol has significantly protect gastric mucosa as ascertained by significant reduction of ulcer area, increases in gastric mucus production, decrease the acidity of gastric content and histology by comparatively decreases gastric mucosal injury, reduction of oedema and leukocyte infiltration of submucosal layer. MCELE was able to decrease the acidity and increase the mucosal defence in the gastric area, thereby justifying its use as an antiulcerogenic agent.

Keywords: *Muntingia calabura*; Gastric ulcer; Mucus; Histology

Introduction

The global incidence of gastric ulcer disease has greatly increased during the last decades. When it acquired to be a natural alternative cure that helps to reduce and treat the gastric ulcer disorders. The etiological factors of this disorder include: stress, smoking, nutritional deficiencies, infections, frequent and indiscriminate use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) [1]. The pathogenesis of gastric ulcers are influenced by several protective and aggressive factors, such as mucus secretion, mucosal barrier, acid-pepsin secretion, blood flow, cellular regeneration and endogenous protective agents (prostaglandins and epidermal growth factor [2]. Although the introduction of proton-pump inhibitors to the classic anti-ulcer therapy had revolutionized treatment of peptic ulcers and other gastrointestinal disorders, but there is still no complete cure for this disease. It has been shown that long term use of these drugs leads to various adverse and side effects. Relapses of the malady, ineffectiveness of different drug regimens and even resistance to drugs are emerging [3]. Consequently, there is a serious obligation to identify more effective and safe antigastric ulcer agents. A widespread search has been thrown to identify new antigastric ulcer remedies from natural sources. Herbs, medicinal plants, spices, vegetables and crude drug substances are considered to be a potential source to combat various diseases including gastric ulcer. In the scientific literature, a large number of medicinal plants with gastric anti-ulcer potential have been reported [4-7].

Muntingia calabura (M. Calabura), which belongs to the family Elaeocarpaceae, is a common roadside tree in Malaysia. It is known locally in Malay as Kerukup Siam. It is native and widely cultivated in warm areas of the Asian region, including Malaysia [8]. This plant is popularly known for its antiseptic and antispasmodic properties besides being a proven hypotensive drug [9]. Various parts of this tree have several documented medicinal uses. Its leaves, barks and flowers are believed to possess medicinal value and is rich in flavonoids, flavones and flavanones, rendering to its potent antitumor activities [10]. Moreover, flowers of *M. calabura* have been used as anti-septic, anti-spasmodic, antidyspeptic, diaphoretic, tranquilizer, tonic and for the treatment of headache, whereas roots are employed as emmenagogue and abortifacient [11]. Infusion of the flower of this plant is drunk as a tranquilliser and tonic [11]. Scientifically, this plant has been proven antinociceptive, anti-inflammatory and anti-pyretic properties [12], potentia antibmicrobial activity [13], potent antityrosinase and antioxidant activities [14,15]), cardioprotective effect [16]. *M. calabura* also inhibited *in vitro* growth of *Candida albicans* and *Cryptococcus neoformans* [17] and cytotoxicity to cultured P-388 cells and some human cancer cell lines [11]. Thus far, there are no data available on the gastroprotective activity of MCELE. The present study was undertaken to evaluate anti-ulcerogenic properties of MCELE in rats.

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Received December 12, 2012; **Accepted** December 28, 2012; **Published** December 31, 2012

Citation: Ibrahim IAA, Abdulla MA, Abdelwahab SI, Al-Bayaty F, Majid NA (2012) Leaves Extract of Muntingia Calabura Protects Against Gastric Ulcer Induced by Ethanol in Sprague-Dawley Rats. Clin Exp Pharmacol S5:004. doi:10.4172/2161-1459.S5-004

Methods

In the present study, used omeprazole as the reference of antigastric ulcer agent, and was obtained from the University Malaya Medical Centre (UMMC) Pharmacy. The drug was dissolved in a carboxymethyl cellulose (0.5% w/v) (CMC) and administered orally to the rats at concentrations of 20 mg/kg body weight (5 ml/kg) [4].

Plant specimen and extract preparation

Muntingia calabura leaves were obtained from Ethno Resources Sdn Bhd, Selangor Malaysia, and identified by comparison with the Voucher specimen deposited in the Herbarium of Rimba Ilmu, Institute of Science Biology, University of Malaya, Kuala Lumpur. The dried leaves were powdered using electrical blender. A hundred grams of the finest powder were soaked in 500 ml of 95% ethanol in a conical flask for 3 days. After three days the mixture was filtered using a fine muslin cloth followed by filter paper (Whatman No. 1) and distilled under low pressure in an Eyela rotary evaporator (Sigma-Aldrich, USA). The dry extract was then dissolved in CMC (0.5% w/v) and administered orally to rats at concentrations of 250 and 500 mg/kg body weight (5 ml/kg body weight) [6].

Acute toxicity test LD50

Sprague-Dawley rats (6 - 8 weeks old) weighed between (150 - 180 g) were obtained from the Animal House, Faculty of Medicine, University of Malaya, Kuala Lumpur (Ethic No. PM/27/07/2010/MAA (R). They were given standard rat pellets and tap water ad libitum. The acute toxic study was used to determine a safe dose of the rhizome extract. Thirty six rats (18 males and 18 females) were assigned equally each into 3 groups labelled as a vehicle (CMC, 0.25% w/v, 5 ml/kg); 2 and 5 g/kg of MCELE preparation, respectively. The animals were deprived of food overnight prior to dosing. Food was withheld for a further 3 - 4 h after dosing. The animals were observed for 30 min and 2, 4, 8, 24 and 48 h after the administration for the onset of clinical or toxicological symptoms. Mortality, if any was observed over a period of 2 weeks. The acute toxicity LD50 was calculated as the geometric mean of the dose that resulted in 100% lethality and that which caused no lethality at all. The animals were sacrificed on the 15th day. Histological, hematological and serum biochemical parameters were determined following standard methods. The study was approved by the ethics committee for animal experimentation, Faculty of Medicine, University of Malaya, Malaysia. All animals received human care according to the criteria outlined in the "Guide for the Care and Use of laboratory Animals" prepared by the National Academy of Sciences and published by the national Institute of health.

Experimental animals for gastric ulcer

Sprague Dawley healthy adult male rats were obtained from the Experimental Animal House, Faculty of Medicine, University of Malaya, and Ethic No. PM/27/07/2010/MAA (R). The rats were divided randomly into 4 groups of 6 rats each. Each rat that weighed between 200 - 225 g was placed individually in a separate cage (one rat per cage) with wide-mesh wire bottoms to prevent coprophagia during the experiment. The animals were maintained on a standard pellet diet and tap water. The study was approved by the Ethics Committee for Animal Experimentation, Faculty of Medicine, University of Malaya, Malaysia. Throughout the experiments, all animals received human care according to the criteria outlined in the "Guide for the Care and Use of laboratory Animals" prepared by the National Academy of Sciences and published by the national Institute of health.

Gastric ulcer-induced by absolute ethanol

The rats were deprived of food for 48 hours before the experiment [4], but were allowed free access to drinking water up till 2 hours before the experiment. Gastric ulcer was induced by orogastric intubation of absolute ethanol (5 ml/kg) [6]. Ulcer control groups were orally administered vehicle (CMC, 0.5% w/v, 5 ml/kg). The reference group received oral doses of 20 mg/kg omeprazole in CMC (5 ml/kg) as positive control. Experimental groups were orally administered . MCELE in CMC solution (5 ml/kg) at doses of 250 and 500 mg/kg. One hour after this pre-treatment all groups of rats were administered with absolute ethanol (5 ml/kg) in order to induce gastric ulcers [4]. The rats were euthanized 60 minutes later [5] under an overdose of xylazin and ketamine anesthesia and their stomachs were immediately excised.

Measurement of mucus production

Gastric mucus production was measured in the rats that were subjected to absolute ethanol-induced gastric lesions. The gastric mucosa of each rat was obtained by gently scraping the mucosa with a glass slide and the collected mucus were weighed by using a precision electronic balance [5,7].

Measurement of acid content of gastric juice (pH)

Samples of gastric juice contents were analysed for hydrogen ion concentration by pH metric titration with 0.1 N NaOH solutions using digital pH meter [4,5].

Gross gastric lesion evaluation

Gastric ulcers of the mucosa appear as elongated bands of hemorrhagic lesions parallel to the long axis of the stomach. Gastric mucosa of each rat was thus examined for damage. The length and width of the ulcer (mm) were measured by a planimeter (10×10 mm^2 = ulcer area) under dissecting microscope (1.8×). The ulcerated area was measured by counting the number of small squares, 2 mm × 2 mm, covering the length and width of each ulcer band. The sum of the areas of all lesions for each stomach was applied in the calculation of the Ulcer Area (UA) wherein the sum of small squares × 4 × 1.8 = UA (mm^2) according to the recommendation of Mahmood et al. [6]. The inhibition percentage (I.0 %) was calculated by the following formula according to the recommendation of Wasman et al. [7].

$$(I\%) = [(UA_{control} - UA_{treated}) \div UA_{control}] \times 100\%$$

Histological evaluation of gastric lesions

Specimens of the gastric walls of each rat were fixed at 10% buffered formalin and processed in a paraffin tissue processing machine. Sections of the stomach were made at a thickness of 5 µm and stained with hematoxylin and eosin for histological evaluation [4,5].

Statistical analysis

All values were reported as mean ± S.E.M. The statistical significance of differences between groups was assessed using one-way ANOVA. A value of $p<0.05$ was considered significant.

Results

Acute toxicity study

Animals treated with MCELE at a dose of 2 and 5 g/kg were kept under observation for 14 days. All the animals remained alive and did not manifest any significant sign of toxicity at these doses. There were no abnormal signs, behavioural changes, body weight changes, or

macroscopic finding at any time of observation. There was no mortality in the above-mentioned doses at the end of 14 days of observation as shown in (Table 2) and (Figure 3). Histological examination of liver and kidney, hematology and serum biochemistry revealed no significant differences between the different groups as shown in . From these results it is concluded that the extract is quite safe even at these higher doses and has no acute toxicity and the oral lethal dose (LD50) for the male and female rats were greater than 5 g/kg body weight.

pH of gastric content and mucus production

The acidity of gastric content in experimental animals pretreated with MCELE was decreased significantly compared to that of the ulcer control group ($p<0.05$). The mucus production of gastric mucosa also increases significantly ($p<0.05$) in animals pretreated with MCELE compared to the ulcer control group (Table 1).

Gross evaluation of gastric lesions

The anti-ulcer activity of MCELE in ethanol-induced gastric lesion model is shown in Table 1. Results showed that rats pre-treated with MCELE extracts before being given absolute alcohol had significantly reduced areas of gastric ulcer formation compared to rats pre-treated with CMC (ulcer control group) (Figure 1) ($p<0.05$). Moreover, the MCELE significantly suppressed the formation of the ulcers and it was interesting to note the flattening of gastric mucosal folds in rats pretreated with 500 mg/kg MCELE (Figure 1). Furthermore, ethanol-induced mucosal damage was significantly and dose dependently reduced in the size and severity by pretreatment of the animals with MCELE. The significant inhibition of gastric ulcer in pretreatment with MCELE was comparable with omeprazole which is a standard drug used for curing gastric ulcer.

Histological evaluation of gastric lesions

Histological observation of ethanol induced gastric lesions in ulcer control group pre-treated with CMC only, showed comparatively extensive damage to the gastric mucosa, and oedema and leucocytes infiltration of the submucosal layer (Figure 2). Rats that received pre-treatment with MCELE had comparatively better protection of the gastric mucosa as seen by a reduction in ulcer area, reduced or absent submucosal edema and leukocyte infiltration (Figure 2).

Discussion

It is well known that gastric lesions induced by ethanol administration appear as multiple-haemorrhagic red bands of different sizes along the glandular stomach. Ethanol is commonly used for inducing ulcer in experimental rats; it leads to intense gastric mucosal damage. Previous studies reported that the ethanol-induced damage to the gastrointestinal mucosa starts with microvascular injury, namely disruption of the vascular endothelium resulting in increased vascular permeability, edema formation and epithelial lifting [18]. Ethanol induces to necrotic lesions in the gastric mucosa by its direct toxic effect, reducing the secretion of bicarbonates and production of mucus [19]. Exposure to ethanol increases the enlargement of cellular damage in a dose-dependent way [6].

Omeprazole is a proton pump inhibitor which has been widely used as an acid inhibitor agent for the treatment of disorders related to gastric acid secretion [20]. Omeprazole has substituted benzimidazoles; it inhibits acid secretion by acting on the hydrogen-potassium exchange ($H^{\pm}$, $K^{\pm}$-ATPase) for the apical plasma membrane of the gastric mucosa [21]. Omeprazole is highly selective for the proton pump and undergoes catalysed conversion into an active form within the acid forming space. The active inhibitors react with SH (thiol) group of the proton pump, resulting in inhibition of acid formation [22].

Results obtained in the current study suggest that MCELE administered showed a protective action against ethanol-induced gastric mucosa injury as demonstrated by the reduction or inhibition of the gastric ulcer area and increased gastric mucous production and decrease the acidity of gastric content. MCELE prevented ethanol induced-gastric damage with mucous production increase. This finding could be interpreted with a correlation to a strengthening of the defence factors of gastric mucosa. It is evident that increased mucus production must have largely contributed to preventive effect of the

Animal Group	Pre-treatment (5 ml/kg dose)	Mucus production	pH of gastric content	Ulcer area (mm)² (Mean ± S.E.M)	Inhibition (%)
1	CMC (Ulcer control)	0.32 ± 0.01^{a}	3.41 ± 0.01^{a}	735.25 ± 2.12^{a}	-
2	Omeprazole (20 mg/kg)	0.56 ± 0.01^{b}	6.81 ± 0.35^{b}	90.33 ± 2.02^{b}	87.71%
3	MCELE (250 mg/kg)	0.52 ± 0.01^{b}	5.78 ± 0.1^{c}	112.5 ± 2.11^{b}	84.7%
4	MCELE (500 mg/kg)	0.58 ± 0.01^{b}	5.86 ± 0.01^{c}	95.08 ± 2.18^{b}	87.07%

All values are expressed as mean ± standard error mean. Means with different superscripts are significantly different. The mean difference is significant at the $p>0.05$ level.

Table 1: Effect of MCELE on ulcer area and inhibition percentage in rats.

Renal function test of rats in acute toxicity study of MCELE.

Dose	Sodium (mmol/L)	Pottasium (mmol/L)	Chloride (mmol/L)	CO_2 (mmol/L)	Anion gap (mmol/L)	Urea (mmol/L)	Creatinine (µmol/L)
Vehicle (CMC.5%)	138.03 ± 0.44	4.96 ± 0.14	102.54 ± 0.15	22.03 ± 0.81	17.66 ± 0.72	5.03 ± 0.41	49.08 ± 0.85
LD (2 g/kg)	137.85 ± 0.43	5.00 ± 0.15	102.63 ± 1.22	21.87 ± 0.19	17.51 ± 0.68	4.98 ± 0.40	48.97 ± 0.83
HD(5 g/kg)	137.72 ± 0.41	4.89 ± 0.14	102.68 ± 0.76	22.13 ± 0.83	17.72 ± 0.75	5.19 ± 0.43	48.86 ± 0.61

Values expressed as mean ± S.E.M. There are no significant differences between groups. Significant value at $p<0.05$

Liver function test of rats in acute toxicity study of MCELE.

Dose	Total protein (g/L)	Albumin (g/L)	Globulin (g/L)	TB (µmol/L)	CB (µmol/L)	AP (IU/L)	ALT (IU/L)	AST (IU/L)	GGT (IU/L)
Vehicle (CMC 0.5%)	71.57 ± 0.64	11.48 ± 0.43	59.97 ± 0.33	1.91 ± 0.16	0.95 ± 0.17	133.27 ± 6.17	51.79 ± 2.25	153.95 ± 2.36	5.13 ± 0.93
5.13 ± 0.93	71.49 ± 0.52	11.63 ± 0.35	59.81 ± 0.35	1.96 ± 0.14	1.00 ± 0.00	133.37 ± 7.03	51.90 ± 1.33	154.07 ± 3.51	5.09 ± 0.83
HD (5 g/kg)	71.72 ± 0.63	11.61 ± 0.18	60.02 ± 0.61	1.88 ± 0.32	1.00 ± 0.00	133.15 ± 6.55	52.04 ± 2.27	153.88 ± 3.33	5.21 ± 0.91

Values expressed as mean ± S.E.M. There are no significant differences between groups. Significant value at $p<0.05$
TB: Total bilirubin; CB: Conjugated bilirubin; AP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase;GGT: G-Glutamyl Transferase.

Table 2: Acute toxicity test.

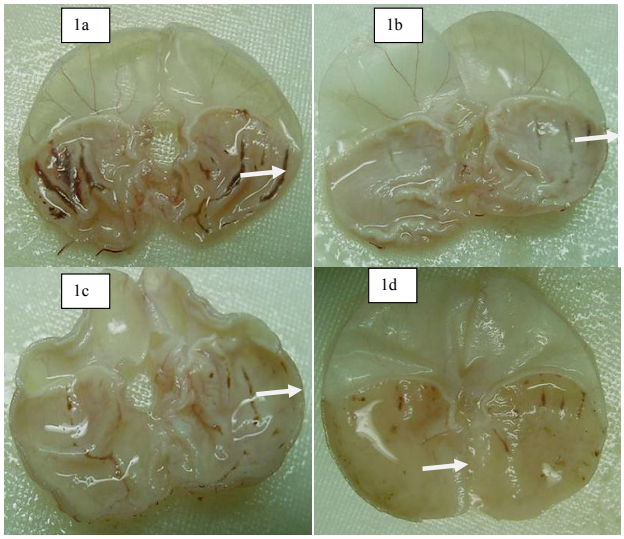

Figure 1: Gross appearance of the gastric mucosa in rats. 1a rats pre-treated with 5 ml/kg CMC (ulcer control). Moderate injuries are seen in the gastric mucosa (arrow). Absolute ethanol produced extensive visible hemorrhagic necrosis of gastric mucosa. 1b rats pre-treated with of omeprazole (20 mg/kg). Injuries to the gastric mucosa are very milder compared to the injuries seen in the ulcer control rats (arrow). 1c rat pre-treated with MCELE (250 mg/kg). Mild injuries are seen in the gastric mucosa. The extract reduces or prevent the formation of gastric lesions induced by absolute ethanol (arrow). 1d rats pre-treated with MCELE 500 mg/kg. Mild injuries to the gastric mucosa are seen, and flattening of the gastric mucosa is seen (arrow).

MCELE. Similar findings exist in the literatures, where plant extracts have been shown to prevent gastric mucosal ulceration in rats [5,7]. The mucus of the gastric wall is thought to play an important role as a defensive factor against gastrointestinal damage [7]. Pretreatment with MCELE significantly decreases the acidity of the gastric content and increases the gastric mucus production. This suggests that gastro-protective effect of MCELE is mediated partly by preservation of gastric mucus production.

Gastric ulcers one of the several diseases that oxidative stress plays an important role to cause, with antioxidants been reported to play a significant role in the protection of gastric mucosa against various necrotic agents [23]. Administration of antioxidants inhibits ethanol-induced gastric injury in rat [24]. MCELE possesses a broad spectrum of biological activities and phytochemical studies showed a high amount of phenols, triterpenes, saponins, steroid, tannins and flavonoids present in the extract of *Muntingia calabura* [14,15,25] and it is speculated that the gastroprotective effect exerted by MCELE could be attributed to its antioxidant property. Several mechanisms of action could be suggested with regards to those groups of chemical compounds, particularly flavonoids and tannins which are present in the *M. calabura* extract.

Antioxidant property of the MCELE may possibly counteract oxidative damage caused by absolute ethanol toxicity. The observed antiulcerogenic activity may be due to its antioxidant effects and appears to strengthen the mucosal barrier, which is the first line of defense against endogenous and exogenous ulcerogenic agents. Previous studies have shown that flavonoids may be related to the antiulcer activity [26], and play a major role in the mechanism of gastroprotection [27]. It could be conceivable that the anti-ulcer activity of this plant could be linked to the flavonoids since flavonoids are reported to protect the mucosa by preventing the formation of lesions by various necrotic agents [28]. It is well known that many flavonoids display antisecretory and cytoprotective properties in different experimental models of gastric ulcer [29]. Flavonoids possess antioxidant properties in addition to strengthening the mucosal defense system through stimulation of gastric mucus secretion [30] and flavonoids can scavenge for the reactive oxygen species (superoxide anions) and free radicals produced by ethanol. These reactive intermediates are potentially implicated in ulcerogenicity [31].

The result of the present study also revealed protection of the gastric mucosa and inhibition of leukocyte infiltration of gastric wall in rats pretreated with MCELE. This plant extract has been shown to contain anti-inflammatory activity [12] and it is speculated that the gastroprotective effect exerted by this plant extract could be attributed to its anti-inflammatory activity. This anti-inflammatory activity could also be a key factor in the prevention of gastric ulcer as reported by Swarnakar et al. [32]. Similarly, Abdulla et al. [4] and Wasman et al. [7] demonstrated that the reduction of neutrophil infiltration was associated with prevention of gastric injury in rats. Oral administration of plant extract before ethanol administration significantly decreased neutrophil infiltration of gastric mucosa [6,7]. Absolute alcohol would extensively damage the gastric mucosa leading to increased neutrophil infiltration into the gastric mucosa. Oxygen free radicals derived from infiltrating neutrophils in ulcerated gastric tissues have an inhibitory effect on gastric ulcers healing in rats [33]. Neutrophils mediate lipid peroxidation through the production of superoxide anions [34]. Neutrophils are a major source of inflammatory mediators and can release potent reactive oxygen species such as superoxide, hydrogen peroxide and myeloperoxidase derived oxidants. These reactive oxygen species are highly cytotoxic and can induce tissue damage [35]. Furthermore, neutrophil accumulation in gastric mucosa

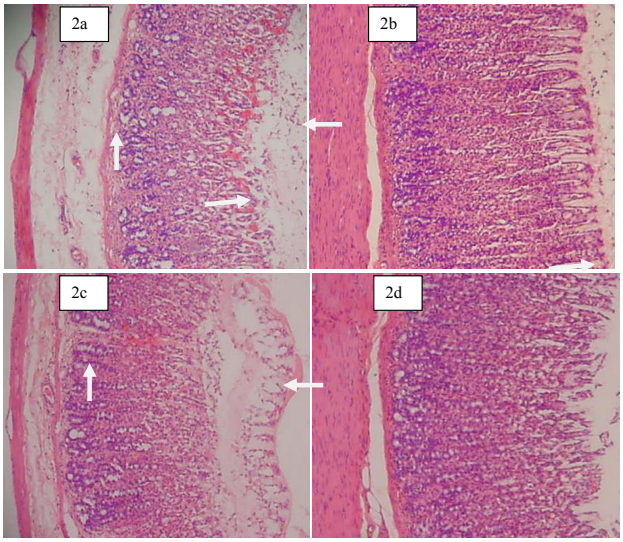

Figure 2: Histological study of the absolute ethanol-induced gastric mucosal damage in rats. 2a rats pre-treated with 5 ml/kg of CMC (ulcer control). There is moderate to severe disruption to the surface epitheliumand necrotic lesions penetrate deeply into mucosa (arrow) and extensive edema of submucosa layer and leucocyte infiltration are present (arrow). 2b rats pre-treated with omeprazole (20 mg/kg). Mild disruption of the surface epithelium mucosa are present but deep mucosal damage is absent. 2c rat pre-treated with MCELE (250 mg/kg). Mild disruption of surface epithelium are present but deep mucosal damage is absent. There is edema and leucocytes infiltration of the submucosal layer. 2d rats pre-treated with MCELE (500 mg/kg). There is mild disruption to the surface epithelium with no edema and no leucocyte infiltration of submucosal layer (H & E stain 20x).

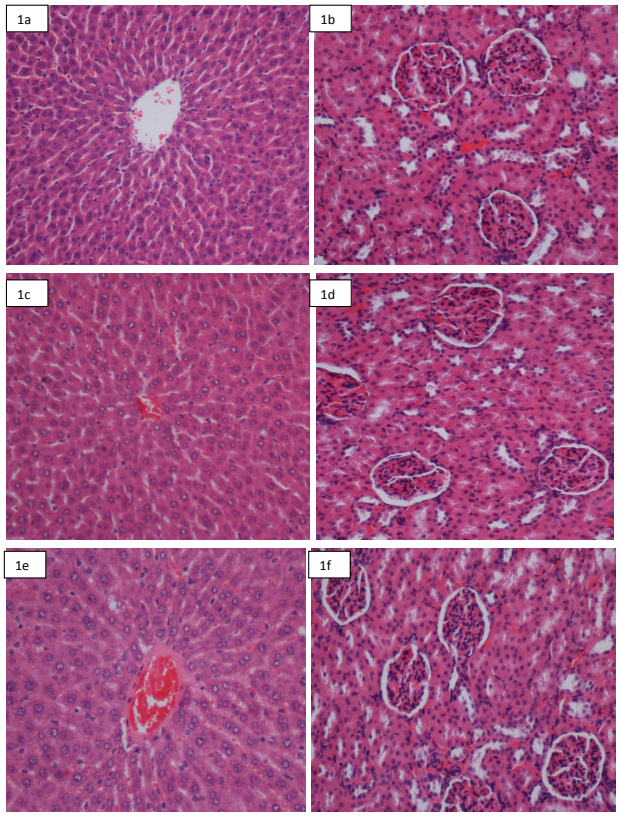

Figure 3: Histological sections of liver and kidney in acute toxicity test. (3a and 3b) Rats treated with 5 ml/kg vehicle (CMC 0.5%). (3c and 3d) Rats treated with 2 g/kg (5 ml/kg) MCELE. (3e and 3f) Rats treated with 5 g/kg (5 ml/kg) MCELE. There is no significant differences in structures of liver and kidney between treated and control groups.

has been shown to induce gastric ulceration [4,27]. Suppression of neutrophil infiltration during inflammation was found to prevent induction of gastric ulcer and enhance gastric ulcer healing [6,7]. Studies have demonstrated the link between the anti-inflammatory and antioxidant activities of the plants. For example, Nitric Oxide (NO) is produced/released under the action of inflammatory stimuli (i.e. ROS) [36]. Inhibition of ROS leads to the reduction of NO production, which has been demonstrated to cause anti-inflammatory and antioxidant activities [37]. The free radical scavenging property may be one of the mechanisms by which these plants' are effective in their ethnopharmacological uses against different ailments.

In the present study, we observed flattening of the mucosal folds which suggests that the gastroprotective effect of MCELE might be due to a decrease in gastric motility. It is reported that the changes in the gastric motility may play a role in the development and prevention of experimental gastric lesions [4,5]. Relaxation of circular muscles may protect the gastric mucosa through flattening of the folds. This will increase the mucosal area exposed to necrotizing agents and reduce the volume of the gastric irritants on rugal crest [6,7]. Ethanol produces a marked contraction of the circular muscles of the rat fundic strip. Such a contraction can lead to mucosal compression at the site of the greatest mechanical stress, at the crests of mucosal folds leading to necrosis and ulceration [4].

Conclusion

In conclusion, MCELE could significantly protect the gastric mucosa against ethanol-induced injury. Such protection was ascertained grossly by increase gastric mucus production and decrease the acidity of gastric content which compared significantly higher in treated groups to ulcer control group and also the reduction of ulcer areas in the gastric wall as well as histology by the reduction or inhibition of edema and leukocyte infiltration of submucosal layers. The data obtained confirm the traditional indications for this herb and present a new therapeutic option for the treatment of gastric ailments. The exact mechanism (s) underlying this anti-ulcerogenic effect remains unknown, but it seems that this extract contains pharmacologically active substances with potent antioxidant and anti-inflammatory activity which increase the mucus production and decrease the acidity of gastric content.

Acknowledgments

This study was financially supported by the University of Malaya through University Malaya Research grant 2009 (UMRG), RG102/09HTM.

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This article was originally published in a special issue, **Pharmacology and Toxicology for Safe and Effective Therapy** handled by Editor(s). Dr. Peter R. Martin, Vanderbilt Psychiatric Hospital, USA