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Dry ripe fruit of *Aegle marmelos as* anti-ulcer agent against ethanol induced gastric mucosal injury

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Abstract: *Aegle marmelos* is cost-effective valuable South Asian tree. The folklore data reported its wide range pharmacological effects. In spite of vast reported work on various parts, the dry ripe fruit extract has not yet been studied for gastric ulcers. Present study is planned to investigate its potential protective effects against ethanol-induced gastric injury in rats. In current study the gastro protective effect of ethanolic crude extract of *A. marmelos* dried ripe fruit at 200, 400 and 800mg/kg body weight were studied in albino rats. Ranitidine used as standard drug (50mg/kg body weight). Absolute ethanol increase the degree of ulceration (UI) in rats while a significant improvement in the level of inhibition against ulceration was observed in test and standard groups as compare to control. Pre-fed test drug exhibited a significant reduction in the sore area (UI), accelerate % age protection and increased of gastric content in dose dependence manner. Test drug at 800mg/kg dose showed marked deduction in mean UI 3.0, significant increase in protection 83% with pH 7.3 (p<0.01). Standard drug exhibited 3.25 UI, 81% protection with pH 7.1. In conclusion, it was found that dry ripe fruit of *A. marmelos* possesses a significant anti-ulcer effect in rats.

Keywords: *A. marmelos*, ethanol induced ulcer model, ulcer index, % protection.

INTRODUCTION

Gastric ulcers or peptic ulcer are open sores in the lining of the stomach that extend to or beyond the mucosa. Worldwide gastric ulcers are regard as the foremost illness characterized by ulceration in the stomach and duodenum (Vomero and Colpo 2014). The pathophysiology of gastric ulceration is multifactorial but is generally considered as a result of an imbalance between the gastric aggressive factors (acid, pepsin, Helicobacter pylori infection and non-steroidal anti-inflammatory agents) and the mucosal protective factors like mucus bicarbonate and blood flow (Escobedo-Hinojosa *et al.,* 2018). Ethanol act as a most common ulcerogenic mediator with its oral consumption well reported for pathogenic effects in stomach of humans and experimental animals (Arab *et al.,* 2015; Shawon and Gautam 2012; Guzmán-Gómez *et al.,* 2018). Intragastrically, ethanol is responsible for severe gastric hemorrhagic erosions therefore this model has been widely utilized for experimental evaluation to find gastro-protective ability of majority of drugs used in the treatment of gastric injuries.

The main focus of treating peptic ulcer is to relieve pain, cure ulcer and prevent its recurrence. The current approach of gastric ulcer management is inhibition of gastric acid secretion, promotion of gastro-protection, blocking apoptosis and stimulation of epithelial cell proliferation for effective healing. The conventional medication employed in the treatment of ulceration comprises of histamine receptor antagonists, prostaglandins analogues, proton pump inhibitors, cytoprotective agents, antacids and anticholinergics. In long term use, majority of drugs produce undesirable effects or drug interactions and may even alter biochemical mechanisms of body that in turns limit their use (Halabi *et al.,* 2014).

Herbal treatment is generally practiced wherein drugs are required to be used for long periods or in chronic cases (Abebaw *et al.,* 2017; Sahoo *et al.,* 2016). Several experimental studies proved that herbs have gastroprotective activities against gastric mucosal injuries induced by ethanol (Sultana *et al.,* 2014). Hence, the efforts are going on to discover an appropriate treatment from natural sources.

Aegle marmelos (L.) Correa generally known as Bael from Rutaceae family, is extensively use in indigenous systems due to its valuable phytochemical constituents (Rahman and Parvin 2014; Asaduzzaman *et al.,* 2016; Rishabha *et al.,* 2012). It is currently cultivated in India, Pakistan, Bangladesh, Srilanka, Burma and Thailand. All parts of *A. marmelos* (leaves, ripe and unripe fruit pulp, seeds, flower, stem bark and root bark) are medicinally useful and possesses remarkable antioxidant, anti-inflammatory, antipyretic, analgesic, antiulcer, hepatic and renal injuries and protection against cardiac activities (Modi and Patel 2013). In spite of all these reported work on various parts of *A. marmelos* the impact of dry ripe fruit extract on gastric ulcer has not yet been studied. Therefore, the present study is designed to explore its potential protective effects against ethanol-induced gastric injury in rats.

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MATERIALS AND METHODS

Plant Material

Dry ripe fruit of *A. marmelos* was obtained from local market and identified by analysis of its macro morphological features and its botanical profile**.** The specimen voucher no Am 0012/2010 was preserved in herbarium of pharmacology lab of PCSIR-labs. The plant material (dry ripe fruit) was cleaned, shade dried, powdered and extracted. In brief 500g of dry fruit powder was extracted with 1.5l ethanol. Filtration was carried out using filter paper. The soaking and filtration steps were repeated on the residue for another two times. The filtrated material from each soaking was pooled together and evaporated using rotary evaporator at 50-60°C under reduced pressure. The resulting dark brown colored semi solid extract was preserved in air tight jar further use.

Animals

For antiulcer activity albino wister rats (male and female) 150-230g were obtained from KLC/PCSIR. The animals were housed in plastic cages bedded with rice husk. The animal room was maintained under standard experimental conditions (Temperature 27±2°C and 12hr light/dark cycle) during experimental period with free access to feed and water. The strategies and procedures were approved by ethical committee (KLC/EC/2020/X) for use of experimental animals of PCSIR Laboratories Complex; Karachi.

Antiulcer Activity and Experimental Design

Albino rats were arranged into five groups of 6 rats each. The animals were fasted for 24 hours before the study but had free access to water. Gastric lesions were induced with absolute ethanol (1ml/200g b.w.) by oral route (Patricia *et al.,* 2015). Group I (control) received vehicle only (distilled water). Group II, III and IV were received test drug at 200, 400 and 800mg/kg body weight respectively by oral route, while Group V received Ranitidine (50mg/kg) as standard drug. After one hour of treatment with test and standard drugs ulcers were induced by oral administration of absolute ethanol in all animal groups. After 30 minutes of ethanol received all animals were scarified and their stomachs were removed carefully.

Measurement of ulcer index

The stomachs were rinsed with distilled water and opened through the grater curvature. pH of gastric contents was determined and mucosa was rinsed with cold distilled water to remove blood debris. Each stomach was pinned on a wooden board for ulcer examinations and assessment. The opened stomachs were examined for hemorrhagic lesions in glandular mucosa. In gastric mucosa, ulcers were appeared as inflammation and as bands of hemorrhagic lesions. Severity of gastric lesions was assessed as follow:

The scoring of each lesion severity was carried out using 0-3 scoring system reported by Akpamu *et al.,* 2013. The severity factor was defined according to the length of the lesions:

No lesions=0
Lesions <1mm length=1
lesions 2-4mm length=2
lesions >4mm length=3

The UI of each rat was calculated as the number of lesions multiplied by their respective severity factor and the mean for each group was taken (table 2) while percentage protection was calculated using the following formula.

$$\text{Percentage protection} = \frac{UIc - UIt}{UIc} \times 100$$

Where,
UIt = UI of treated group and
UIc = UI index of control group

pH measurement

The pH was noted by means of pH strips by matching the color obtained with that of the reference standard (Ingale *et al.,* 2016).

STATISTICAL ANALYSIS

The data was presented as mean ±SEM for all groups. Student 't' test was used for statistical analysis of data. Results were considered to be statistically significant at $p<0.05$ (https://www.socscistatistics.com, https://www.graphpad.com).

RESULTS

Administration at 200, 400 and 800mg/kg extract of *A. marmelos* exhibited significant reduction in the mean UI ranging from 9.38±1.32 to 3±1.58 from 200 to 800mg/kg dose as compare to control group animals 17.32±8.01. The extract showed dose dependent gastro protective effects with percent protection from 46% to 83% with raised in pH 5.4 to 7.3. The extract (800mg/kg) showed highly significant and slightly better gastro protective effects with UI 3.0±1.5 and 83% protection over ranitidine that showed UI 3.25±1.66 with 81% protection, and 7.1 pH (table 2).

DISCUSSION

In current study absolute alcohol produces remarkable injuries in gastric mucosa of rats, characterized by elongated macroscopic lesions with intense hemorrhage and hyperemia. Ethanol induced gastric ulcer model is selected because it is a key experimental model usually utilize for preclinical evaluation of potential antiulcer agents (Arab *et al.,* 2015). Alcohol damages gastric mucosa by increasing mucosal permeability disturbs gastric secretion, microvascular changes and may provoke

bleeding and necrotic tissue injuries of uniform severity within few minutes after its administration (Gupta *et al.,* 2021). Distinctive healing retailers together with plant extracts are used that inhibit the gastric acid secretion or to encourage the mucosal protection mechanisms through growing mucus production, stabilizing the surface epithelial cells or interfering with the prostaglandin synthesis.

To regain the stability between aggressive factors and defense mechanism of body, various therapeutic agents including herbal extracts are utilize that inhibit the gastric acid secretion or to promote the mucosal defense mechanisms by increasing mucus production, stabilizing the surface epithelial cells or interfering with prostaglandin synthesis (Tambe and Bhambar 2016). The results of present study recognized *A. marmelos* as an effective anti ulcerogenic agent. It significantly protected the gastric mucosa by reduced values of ulcer index, increase in % protection and pH in dose depended manner as compared to control group. The test drug at 200, 400 and 800mg/kg dose exhibited 9.3±1.3 (p<0.05), 4.9±2.6 (p<0.01), 3.0±1.5 (p<0.01) UI with 46, 71, 83% ulcer protection and pH 5.4, 6.2 and 7.3 respectively. It was observed that the intragastric administration of absolute ethanol (1ml/200g for 30min exposure) in control group causes severe hemorrhagic gastritis with high UI score 17.33±8.01 and pH 2.9, indicating several linear hemorrhagic ulcers and multifocal erosions (table 2). Test drug at highest dose found comparable with that of the standard drug showing UI 3.25±1.6 (p<0.01) with 81% protection and pH 7.1 (fig. 1). The dry ripe fruit of *A. marmelos* exhibits equal or slightly more valuable antiulcer results in compression with previously reported antiulcer results of its various parts at same dose. A study conducted by Rahman *et al.,* 2018 reported 19.3 ulcer index with 37.2% protection at 200 and 400mg/kg dose of *A. marmelos* leaves aqueous extract in same model. One more similar model study of *A. marmelos* ethanolic leaf extract (400mg/kg) reported 56.33% protection (Rahman *et al.,* 2016). Our findings on dried ripe fruit of same plant showed 46 and 71% protection at 200 and 400mg/kg respectively in same ulcer induce model. A Study conducted on *A. marmelos* unripe fruit aqueous extract at 300 and 500mg/kg showed 8.58, 2.18 ulcer index with 36.44 and 83.85% protection respectively (Sharmila *et al*., 2013) while our results on dried ripe fruit showed 9.39 and 4.97 ulcer index with 46 and 71% protection at 200 and 400mg/kg dose. It is well accepted that natural antioxidants are vital for restoring gastric tissue. Along with protecting gastric mucosa from cell damage due to oxidative stress they also promote the protective systems against degenerative diseases (Brito *et al.,* 2018; Klein-Júnior *et al.,* 2012; Hussain *et al.,* 2015; Pan *et al.,* 2008; Alirezaei *et al.,* 2012; Rishabha *et al.,* 2012**).** Many scientific studies reported *A. marmelos* leaves, seeds and fruits (methanol, ethanol and aqueous extracts) have strong antioxidant activity (Kumar *et al.,* 2016; Raja and Khan 2017; Rajan *et al.,* 2011; Kejariwal 2016; Karumaran *et al.,* 2016; Bristy *et al.,* 2017). Previously we had also reported its strong antioxidant activity (Rahman *et al.,* 2016). In connection with well demonstrated previous studies and our reported activity too, we can conclude that the significant capability of test drug for inhibiting gastric lesions formed by ethanol might be related to the activation of antioxidant system that may contribute to their preventive benefits in the development of gastric ulcers.

Table 1: Rating scale for ulcer diameter

Sr. #	Ulcer diameter	Rating scale
1	No ulcer	0
2	≤1 mm	1
3	2-4mm	2
4	>4 mm	3

Table 2: Effect of *A. marmelos* dry ripe fruit extract on UI and pH of gastric content

Animal groups	Pre-treatment	Ul (mm2)	Gastric pH
1.	control	*17.32±8.01*	2.9
2.	*A. marmelos* 200mg/kg	*9.38±1.32**	5.4
3.	*A. marmelos* 400mg/kg	*4.97±2.60***	6.2
4.	*A. marmelos* 800mg/kg	*3.0±1.58***	7.3
5.	Ranitidine 50mg/kg	*3.25±1.66***	7.1

The values are expressed as the mean±SEM, n= 6. *p<0.05 and **p<0.01 when compared with vehicle control group

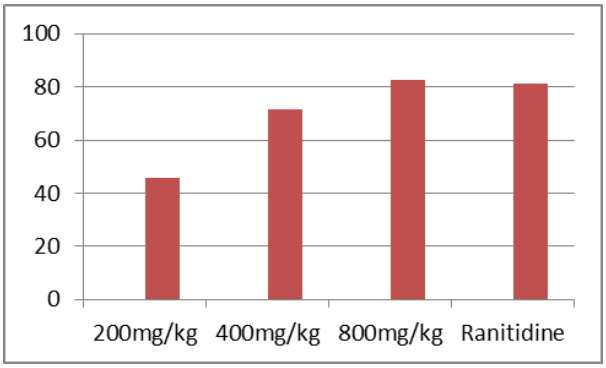

Fig. 1: *A. marmelos* ulcer protection (% protection)

Alcohol affects the gastric mucosa topically by disrupting its barrier and alters the mucosal flow in gastric mucosa that in turn causes ulcers formation. Therefore acid suppression and increase mucus secretion is main focus in majority of pharmacological treatments designed to stop or cure gastric ulcers (Rahim *et al.,* 2014). Singh and Guha 2012 reported the anti secretary effect of aqueous extract of *A. marmelos* ripe fruit pulp by exhibiting decline in amount of gastric juice secretion, gastric acid secretion and an increase of pH within the gastric luminal milieu along with increased mucus content of gastric juice. Another study (Ramakrishna *et al.,* 2015) on *A. marmelos* unripe fruit methanolic extract against HP-LPS

induced gastric ulcer model also reported anti secretary role by reducing acid secretion and pepsin levels in the damaged stomach. Sharmila *et al.,* 2013 reported *A. marmelos* unripe fruit aqueous extract for decrease in gastric volume, total acidity, free acidity, ulcer index and increased pH of gastric juice in dose dependent manner. Current study results coincide with all these findings as pretreatment with *A. marmelos* from lower to high dose exhibit decline UI, increases % protection and pH representing its antisecretory effect. All these effects of *A. marmelos* may act as its antiulcerogenic and cytoprotective effect by increasing the viscosity of the gastric mucus and decreasing pepsin activity.

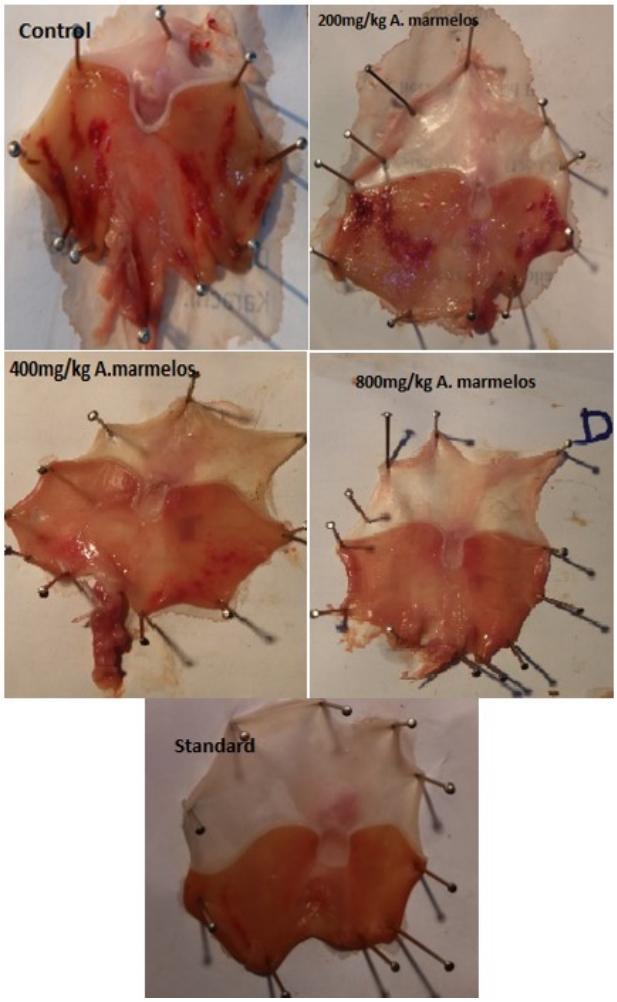

Fig. 2: Effect of different doses of *A. marmelos* on the severity of gastric lesion (gross analysis)

Scientific documents extensively confirmed that the phytoconstituents like flavonoids, tannins, glycosides, triterpenoids and saponin act as gastro protective agents (Borelli and Izzo 2000; Kumar *et al.,* 2013; Bandhopadhyay *et al.,* 2002; Pandian *et al.,* 2002). The reported phytochemical constituents in *A. marmelos* are triterpenoids, glycosides, saponins, quercetin, tannins, βsitosterol, vitamin E, beta-carotene, Luvangetin a pyranocoumarin, Cineole, and amino acids (Pasquale *et al.,* 1995; Krishnakanth *et al.,* 2017; Ramakrishna *et al.,* 2015). Thus the potent antiulcer activity of tested drug can be justified with the synergistic effect of these chemicals. Sharma *et al.,* 2011 reported reduction in volume of gastric juice, free acidity and total acidity, along with increase in pH in methanolic and aqueous extract of *A. marmelos* seeds due to the presence of quercetin like (Flavonoid) contents. Dried ripe fruit extract of *A. marmelos* also containing seeds therefore such type of flavonoid may also be present in test drug that exhibited ulcer curing activity in test animals. Ranitidine used as a standard antiulcer drug. It acts as antiulcer by decreasing the secretion of gastric aggressive factors, free acidity, total acidity and pepsin content along with increased the mucus secretion (Khare *et al.,* 2008; Ignatius *et al.,* 2013). Test drug also showed antiulcer effects on almost similar mechanism of standard drug Ranitidine. All these reported statements strengthen our results. Our observation is consistent with the findings of several other previous reported studies on ethanol induced ulcer animal model studies. *P*re-fed *A. marmelos dry ripe fruit* extract is able to protect the mucosal layer of the stomach from destructive causes.

CONCLUSION

In conclusion, to the best of our information for the first time, we have demonstrated that dry ripe fruit of *A. marmelos* has gastroprotective action towards experimentally induced ulcers in rats. Its gastroprotective effects may be due to its antisecretory and cytoprotective activities. However further experiments are needed to elaborate the molecular mechanism(s) of its anti-ulcer activity.

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