



ANTI-ULCEROGENIC EFFECT OF *MORINDA CITRIFOLIA* IN VARIOUS EXPERIMENTAL MODELS

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ABSTRACT

Morinda citrifolia is a member of the Rubiaceae. It is a Shrub or compacted to twisted small tree up to 8 m high with square stems and large stipules between nodes and petioles. Leaves are opposite, petiolate, glossy, mostly ovate, 15-35 cm long. Flowers white, up to 15 mm long, with a tubular corolla and 5 spreading lobes, the flowers borne on a globose syncarp. Fruit a large fleshy syncarp up to 15 cm long, at first green but becoming white, juicy, and pungent when mature. Flowers and fruits are available throughout the year. To investigate the phytoconstituents, acute oral toxicity and anti-ulcer profile of the Ethanol extract of *Morinda citrifolia* leaf extract in albino rats. Ethanolic extract at the doses of 200 and 400 mg/kg p.o administered to evaluate anti-ulcer activity by using Ethanol, indomethacin, and cold-restraint stress induced gastric ulcer models in Albino rats. Ethanol extract gave positive results for the alkaloids, reducing sugars, triterpenoids, and flavonoids. Study on acute toxicity of extract was found to be safe at the doses 2000mg/kg p.o. Ethanol extract dose dependent inhibition in ethanol induced gastric lesions, ethanol extract showed 68.3% % protection at 400 mg/kg, and 51.7% protection at 200 mg/kg, In indomethacin induced gastric lesions, Ethanol extract showed 75.02% protection at 400 mg/kg and 45.86% protection at 200 mg/kg, it also dose dependent inhibition in Cold-restraint stress induced gastric lesions, ethanol extract showed 75.45% protection at 400 mg/kg, and 50.34% protection at 200 mg/kg. All the results are found to be statistically significant ($p \leq 0.05$). Hence we suggest that ethanol extract possess anti-ulcerogenic properties that may be due to cytoprotective mechanism. These results support the ethnomedical uses of the plant in the treatment of gastric ulcer.

Keywords: *Morinda citrifolia* (L.), Antiulcer Activity, Ethanol, Indomethacin, Cold-restraint stress.

INTRODUCTION

Peptic ulcer disease affect a large portion of the world population and are induced by several factors, including stress, smoking, nutritional deficiencies, and ingestion of non-steroidal anti-inflammatory drugs [1]. The pathophysiology of these ulcers involves an imbalance between offensive (acid, pepsin, and *Helicobacter pylori*) and defensive factors (mucin, prostaglandin, bicarbonate, nitric oxide and growth factors). Today, there are two main approaches for treating peptic ulcer. The first deals with reducing the production of gastric acid and the second with re-enforcing gastric mucosal protection [2,3]. There has been a rapid progress in the understanding of the pathogenesis of

peptic ulcer. Modern approach to this includes proton pump inhibitors, histamine receptor blockers, drugs affecting the mucosal barrier and prostaglandin analog [4]. Development of tolerance and incidence of relapses and side effects on clinical evaluation make their efficacy arguable. This has been the basis for the development of new antiulcer drugs, which includes herbal drugs.

Morinda citrifolia is a herbaceous member of the family Rubiaceae. It is a Shrub or compacted to twisted small tree up to 8 m high with square stems and large stipules between nodes and petioles. Leaves are opposite, petiolate, glossy, mostly ovate, 15-35 cm long. Flowers

white, up to 15 mm long, with a tubular corolla and 5 spreading lobes, the flowers borne on a globose syncarp. Fruit a large fleshy syncarp up to 15 cm long, at first green but becoming white, juicy, and pungent when mature. Flowers and fruits are available throughout the year. It is used as uterine muscle relaxant, analgesic, hypotensive, antiascaris, antibacterial. To treat swellings, boils, ringworm, and rheumatism. Liquid pressed from young fruit is snuffed into each nostril to treat bad breath and raspy voice. It is also used in the treatment of mouth ulcers, haemorrhoids, hernia or swollen testicles, headaches, pain caused by barb of poisonous fish, removal of a splinter, childbirth, diabetes, diarrhoea and dysentery, fever, intestinal worms, filariasis, leprosy, and tuberculosis. In Fiji, the leaves are used as a poultice for broken bones and sprains. An infusion of the root is used in treating urinary disorders and young fruits are used to treat high blood pressure. In Tonga, infusion of the bark/leaves is used to treat stomachache. The leaves are used to treat sties. In New Guinea, the root is rubbed onto centipede bites. An infusion of the root bark is used to treat skin diseases. It is also used to treat sores on the feet. The bark is used in a treatment to aid childbirth. In Micronesia, ulcerated sores on the feet are treated with remedies made from the fruit. The root is crushed and mixed with oil and is used as a smallpox salve. Polynesians apply the leaves to cuts, abscesses and inflammations. In Samoa, Tonga and Futuna, the crushed fruit is used in treating sore throat and toothache. Tahitians use the plant to treat tonsillitis, abdominal swellings, burns, swellings below the tongue and inflammations of fingers and toes [5-12]. From the source of literature documentation and relevant traditional approaches on plant drugs, the present investigation was carried out to investigate the constituents and anti-ulcer profile of the ethanol extract of *Morinda citrifolia* (EEMC) is being reported here.

MATERIALS AND METHODS

Plant material:

The whole plant of *Morinda citrifolia* was collected from Tirumala hills, Tirupati, Andhra Pradesh, India. It was identified and authenticated by Prof. Jayaraman, Taxonomist, Tambaram, Chennai, Tamilnadu, India. A voucher specimen (FM-P-06-S3) has been kept in our laboratory for future reference.

Preparation of plant extract:

The collected plant leaves was dried at room temperature, pulverized by a mechanical grinder, sieved through 40 mesh. About 120g of powdered materials were extracted with petroleum ether (60°-80°C) using Soxhlet apparatus. The extraction was carried out until the extractive becomes colourless. The extracts were then concentrated and dried under reduced pressure. The solvent free semisolid mass thus obtained is dissolved in tween 80 and used for the

experiment. The percentage yield of prepared extract was around 8.3% w/w.

Phytochemical Screening:

The phytochemical examination of ethanol extract of *Morinda citrifolia* was performed by the standard methods [13].

Animals Used:

Albino rats (150–200 g) of either sex were maintained in a 12 h light/dark cycle at a constant temperature 25 °C with free access to feed (Sai durga feeds and foods, Bangalore) and water. All animals were fasted prior to all assays and were allocated to different experimental groups each of 6 rats. Moreover the animals were kept in specially constructed cages to prevent coprophagia during the experiment. All experiments were carried out according to the guidelines for care and use of experimental animals and approved by Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA). Ethical committee clearance was obtained from IAEC (Institutional Animal Ethics Committee) of CPCSEA.

Acute toxicity study:

The acute toxicity of Ethanolic extract of *Morinda citrifolia* leaves was determined as per the OECD guideline no. 423 (Acute Toxic Class Method). It was observed that the test extract was not lethal to the rats even at 2000mg/kg dose. Hence, 1/10th (200mg/kg) and 1/5th (400mg/kg) of this dose were selected for further study [14].

Antiulcer activity:

Ethanol induced gastric ulcer:

Animals were randomly divided into four groups each of 6 rats. Group I treated with 4% v/v aqueous tween 80 (10 ml/kg p.o), Group II & III treated with Ethanol extract of *Morinda citrifolia* (200 and 400mg/kg p.o) respectively for 14 days and Group IV treated with Omeprazole (20 mg/kg p.o) were administered 30min prior to induction of gastric ulcer. On the 14th day, Gastric ulcers were induced with ethanol at a dose of 8ml/kg [15] administered to all group by orally. The animals were anaesthetized 6 h with ether and stomachs were incised along the greater curvature and the ulcer index for each rat was taken as the mean ulcer score.

Indomethacin induced gastric ulcer:

Animals were divided into four groups each of six rats. Group I treated with 4% v/v aqueous tween 80 (10 ml/kg p.o), Group II & III treated with Ethanol extract of *Morinda citrifolia* (200 and 400mg/kg p.o) respectively for 14 days and Group IV treated with Omeprazole (20 mg/kg p.o) were administered 30min prior to induction of gastric ulcer. On the 14th day, Gastric ulcer were induced with indomethacin (40 mg/kg p.o) administered to all

groups after fasting for 24 h. The animals were sacrificed 4 h after treatment with the ulcerogenic agent [16] to assess the antiulcer activity and ulcer index were examined on the dissected stomachs as described below.

Cold-restraint stress-induced ulcers:

Animals were divided into four groups each of six rats. Group I treated with 4% v/v aqueous tween 80 (10 ml/kg p.o), Group II & III treated with Ethanol extract of *Morinda citrifolia* (200 and 400mg/kg p.o) respectively for 14 days and Group IV treated with Omeprazole (20 mg/kg p.o). On the 14th day, One hour after drug treatment, the experimental rats were immobilized by strapping the hind limbs on a wooden plank and kept for 1 h 30min, at temperature of 3–5 °C [17]. One hour later, the animals were sacrificed by cervical dislocation and ulcers were examined on the dissected stomachs as described below.

Measurement of ulcer index:

The stomachs were excised and were examined for haemorrhagic lesions in glandular mucosa. Immediately after the animals were sacrificed, their stomachs were dissected out, cut along the greater curvature and the mucosa were rinsed with cold normal saline to remove blood contaminant, if any. The sum of the length (mm) of all lesions for each stomach was used as the ulcer index (UI), and the percentage of inhibition (%I) was calculated as described by [18] using the following formula:

$$\%I = \frac{(USc - USt)}{USc} \times 100$$

Where USc = ulcer surface area in control and USt = ulcer surface area in treated animals.

Histopathological studies:

The freshly excised stomachs were washed with saline and preserved in 10% formaldehyde solution for histopathological studies. The sections of stomachs stained with hematoxylin and eosin, were assessed for histopathological changes such as congestion, edema, haemorrhage and necrosis [19]. The microscopic slides were photographed.

Statistical analysis:

The data were expressed as mean ± standard error mean (S.E.M). The Significance of differences among the group was assessed using one way and multiple way analysis

of variance (ANOVA). The test followed by Dunnett’s test p values less than 0.05 were considered as significance.

RESULTS

Phytochemical investigation:

The results of preliminary phytochemical investigation of the ethanol extract of *Morinda citrifolia leaves* (Ethanol extract) shows the presence of alkaloids, reducing sugars, triterpenoids, and flavonoids.

Acute toxicity study:

Acute toxicity study in which the animals treated with the ethanol extract at a higher dose of 2000 mg/kg did not manifest any significant abnormal signs, behavioral changes, body weight changes, or macroscopic findings at any time of observation. There was no mortality in the above-mentioned dose at the end of the 14 days of observation.

Effect of Ethanol extract on gastric ulcer induced by Ethanol:

The ethanol extract showed significant anti-ulcer effect against ulcers induced by ethanol in a dose dependent manner. In ethanol induced ulcer model, ethanol extract at a dose of 200 and 400 mg/kg body weight showed protective effect of 51.7 and 68.3 %, respectively, where as Omeprazole showed protection index of 77.3% at a dose of 20 mg/kg body weight (Table -1).

Effect of Ethanol extract on gastric ulcer induced by Indomethacin:

The ethanol extract showed significant anti-ulcer effect against ulcers induced by *Indomethacin* in a dose dependent manner. In *Indomethacin* induced ulcer model, ethanol extract at a dose of 200 and 400 mg/kg body weight showed protective effect of 45.86 and 75.02%, respectively, where as Omeprazole showed protection index of 81.20% at a dose of 20 mg/kg body weight (Table -2).

Effect of ethanol extract on gastric ulcer induced by Cold-restraint stress:

The ethanol extract showed significant anti-ulcer effect against ulcers induced by *Cold restraint stress* in a dose dependent manner. In the gastric ulcer induced by *Cold-restraint stress*, ethanol extract at a dose of 200 and 400 mg/kg body weight showed again significant activity. Ethanol extract at a dose 200 and 400 mg/kg body weight showed dose-dependent protective effect of 50.34 and 75.45% respectively, where as Omeprazole showed protection effect of 80.50% at a dose of 20 mg/kg body weight, in both the above models. (Table-3).

Table 1: Effect of Ethanol extract of *Morinda citrifolia L. (EEMC)* in ethanol (8 ml/kg) induced gastric ulcer in rats

Group	Design of Treatment	Ulcer Index	Percentage Inhibition (% I)
I	Control (4% v/v aqueous tween 80, 10 ml/kg b.w) p.o	10 ± 0.58	---
II	EEMC (200mg/kg b.w) p.o	4.83 ± 0.17*	51.7
III	EEMC (400mg/kg b.w) p.o	3.17 ± 0.31**	68.3
IV	Omeprazole (20mg/kg b.w) p.o	2.27 ± 0.31**	77.3

Data are represented as mean ± S.E.M. Statistical analysis was done by one-way ANOVA followed by Dunnett’s multiple comparison test. *P < 0.01 and **P < 0.001 as compared to control (n = 6 in each group). B.W=Body weight

Table-2: Effect of Ethanol extract of *Morinda citrifolia* L. (EEMC) in indomethacin (40 mg/kg) induced gastric ulcer in rats

Group	Design of Treatment	Ulcer Index	Percentage Inhibition (% I)
I	Control (4% v/v aqueous tween 80, 10 ml/kg b.w) p.o	18.14 + 0.22	-
II	EEMC (200mg/kg b.w) p.o	9.82 + 1.03*	45.86
III	EEMC (400mg/kg b.w) p.o	4.53 + 0.21**	75.02
IV	Omeprazole (20mg/kg b.w) p.o	3.41 + 0.32**	81.20

Data are represented as mean \pm S.E.M. Statistical analysis was done by one-way ANOVA followed by Dunnett's multiple comparison test. *P < 0.01 and **P < 0.001 as compared to control (n = 6 in each group). B.W=Body weight.

Table -4: Effect of Ethanol extract of *Morinda citrifolia* L. (EEMC) on Cold-restraint stress induced Gastric ulcer in Rats.

Group	Design of Treatment	Ulcer Index	Percentage Inhibition (% I)
I	Control (4% v/v aqueous tween 80, 10 ml/kg b.w) p.o	8.72 + 2.3	-
II	EEMC (200mg/kg b.w) p.o	4.33 + 0.8*	50.34
III	EEMC (400mg/kg b.w) p.o	2.14 + 0.6**	75.45
IV	Omeprazole (20mg/kg b.w) p.o	1.70 + 0.5**	80.50

Data are represented as mean \pm S.E.M. Statistical analysis was done by one-way ANOVA followed by Dunnett's multiple comparison test. *P < 0.01 and **P < 0.001 as compared to control (n = 6 in each group). B.W=Body weight.

DISCUSSION & CONCLUSION

The ethanolic extracts from the leaves of *Morinda citrifolia* showed protective effects against ethanol, indomethacin, and cold restraint stress-induced gastric mucosal damage. The anti-ulcer effect of ethanol extract was tested against gastric lesions induced by ethanol, the experimental model related to lesion pathogenesis with production of reactive oxygen species. Reactive oxygen species are involved in the pathogenesis of ethanol-induced gastric mucosal injury in vivo [20]. *Morinda citrifolia* prevented the mucosal lesions induced by ethanol. The gastric mucosal protection against ethanol can be mediated through a number of mechanisms that include enhancement of the gastric mucosal defense through increase in mucus and/or bicarbonate production, reducing the volume of gastric acid secretion or by simply neutralizing the gastric acidity [21]. Ethanol extract may either reduce the gastric acid secretion or enhance the barrier defence of the mucosal wall. Ethanol extract dose dependent inhibition in ethanol induced gastric lesions [22] (Table 1).

Their anti-ulcerogenic potency was tested against indomethacin-induced ulcer. Indomethacin is a cyclooxygenase inhibitor which suppresses gastroduodenal bicarbonate secretion, reduces endogenous prostaglandin biosynthesis and disrupts the mucosal barrier as well as mucosal blood flow in animals [23]. It is also well known that prostaglandins synthesized in large quantities by the gastrointestinal mucosa can prevent experimentally induced ulcers by ulcerogens. Thus, when the ulcers lesions are induced by indomethacin, the cytoprotective effect of the anti-ulcer agent can be mediated through endogenous prostaglandins [24]. The results obtained show that the mean ulcer index was significantly reduced in the ethanol extracts from the leaves of *Morinda citrifolia* treated groups, compared to their respective controls. Ethanol extract may

be stimulate the secretion of prostaglandins or possess prostaglandins like-substances (Table 2).

In order to probe the effectiveness of ethanol extract in preventing gastric ulcer and also assess their antisecretory activity, they were tested against cool stress induced ulcer. cold restrained stress- induced ulcers are results of auto digestion of the gastric mucosal barrier probably due to excess production and accumulation of HCl in the stomach. The current data clearly demonstrated that, ethanol extract in a dose-dependent manner decreased hydrogenionic concentration suggesting that the pharmacological mechanism has a relationship to antisecretory activity (Table 3).

To further confirm its anti-ulcerogenic effect ethanol extract was evaluated for Cold-restraint stress - induced ulcer model. Gastric ulceration induced by stress is probably mediated by the presence of acid, increase in gastric motility, [25] mast cell degranulation[26], decreased gastric mucosal blood flow [27], decreased prostaglandin synthesis [28] and augmented excretion of glycoproteins in the mucus [29]. Moreover, stress-induced ulcer can be prevented partially or entirely by vagotomy; vagal over activity has been suggested to be the principal factor in stress-induced ulceration [30]. Any of these factors could play a role in genesis of stress-induced ulcers. Oral administration of the ethanolic extracts of *Morinda citrifolia* showed dose dependent inhibition of gastric ulceration induced by Cold-restraint stress.

Phytochemical studies of the ethanol extract revealed the presence of flavonoids, alkaloids and triterpenoids which may be responsible for the anti-ulcer properties. Many compounds from these chemical classes such as nimbidine, ursolic acid, oleanolic acid, qualetin, diosmin, wogonin and sophoradine [31-34] have been shown to possess anti-ulcer properties.

The ethanolic extracts of *Morinda citrifolia* at a dose of 400mg/kg showed similar activity to that of omeprazole (a proton pump inhibitor). The gastro protective effect of omeprazole is mediated through block of acid secretion by inactivation of H⁺/K⁺-ATPase [35]. This study reveals that the ethanol extract are potent inhibitors of gastric mucosal lesions caused by ethanol, indomethacin, and cold-restraint stress in rats.

Further, our results fortify the ethanopharmacological importance of ethanol extract as an anti-ulcer agent. Etiology of ulcers produced in different ulcer models is diverse. The study was concluded ethanol extract and its active constituents may emerge as more effective therapeutic agent to counter gastric ulcer incidence.

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