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EFFECT OF ETHANOL EXTRACT FROM *MORUS ALBA*LEAVES SUPPLEMENTATION ON GASTRIC TISSUE GLUTATHIONE LEVEL IN INDOMETHACIN INDUCED ULCERS IN RATS

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Keywords:

Morus alba, Moraceae, GSH, gastric wall mucus, Indomethacin Induced Ulcers.

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ABSTRACT: Context: The leaves *Morus alba* have been traditionally used in Asian countries for treatment of different ailments. **Objective:** Present study was undertaken to evaluate the effect of ethanol extract from *Morus alba* leaves supplementation on gastric tissue glutathione level in indomethacin induced ulcers in rats. **Materials and Methods:** Ethanol extract from *Morus alba* leaves was administered at the doses 200 and 400 mg/kg/day, p.o. for seven days. Ulceration was induced by giving indomethacin. Ulcer index, gastric GSH level, gastric wall mucus level was estimated. The functioning of liver was also assayed. **Results:** The effects ethanol extract from *Morus alba* leaves were significant and comparable to reference treated group of rats. The gastric GSH levels were replenished by *Morus alba* leaves in 400 mg/kg. **Conclusion:** From this study it was concluded that ethanol extract from *Morus alba* leaves possess significant ulcer protection by replenishing gastric GSH and increasing gastric mucus level.

INTRODUCTION: Gastric ulcer is a major disease of gastrointestinal system which affects 10% of the world population with different etiologies [1]. Gastric ulcers of common pathologies may be induced by a variety of factors, such as stress, smoking, and noxious agents, including non-steroidal anti-inflammatory drugs (NSAIDs); are worldwide used for the treatment of pain, rheumatic and cardiovascular diseases [2].

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Also NSAID sare the one of the causing agent used in the gastroprotective activity in experimental animals [3].

Plants produce a vast and diverse assortment of organic compounds or secondary metabolites, the great majority of which do not appear to participate directly in growth and development are often referred to as natural products [4]. Phytochemicals rich plants are dependent traditionally to cure various maladies. *Morus alba* L. (Family: Moraceae)is dominantly one of them and commonly known as mulberry [5]. Generally, it is used as foliage to feed the silkworms (*Bombyx mori* L.) and ruminants [6, 7]. Leaves of the plant contain protein, crude fibres, neutral dietary fibres [8], moran 20K and 1-deoxynojirimycin (DNJ), isoprene-

substituted flavanones: kuwanon G and kuwanon C [9, 10]. Kuwanon C, mulberrofuran G, albanol B [11, 12], quercetin 3-(6-malonylglucoside), rutin, isoquercitrin, astragalin are the flavonol glycosides present in the *Morus alba* leaves [13]. 1-Deoxynojirimycin (DNJ), a polyhydroxylated piperidine alkaloid present in both leaves and bark, known to be one of the most potent a-glycosidase inhibitors [14, 15]. Mulberry (*M. alba*) leaf extract provides a viable treatment for Alzheimer's disease through the inhibition of amyloid beta-peptide (1-42) fibril formation and attenuation of amyloid beta-peptide (1-42)-induced neurotoxicity [16]. The extract of mulberry leaves exhibited free radical scavenging and antioxidant activities responsible for depigmentation [17, 18].

It suppresses the overproduction of melanin in skin by inhibiting tyrosinase [19]. Hot water extracts of Mulberry leaves possess anti-allergic potential [20]. *M. alba* leaves and its subfractions (chloroform, butanol, and aqueous fractions) inhibited NO production and significantly decreased the production of TNF-a in LPS activated RAW264.7 macrophages [21]. Abdulla *et al*. had studied effects of leaves extract on ethanol induced gastric ulcer in rats [22].

On the basis of literature review, the aim of the present is to evaluate the effect of ethanol extract from *Morus alba* L. (family: Moraceae) leaves supplementation on gastric tissue glutathione level in indomethacin induced ulcers in rats.

MATERIALS AND METHODS:

Collection of Plant material:

The fresh leaves of *Morus alba*L. were collected in February 2011, from the garden of the institute. The plant materials were taxonomically identified and authenticated by Dr. D. C. Saini, Scientist E at Birbal Sahni Institute of Palaeobotony, Lucknow with reference no. 13597.

Preparation of Extract:

Fresh leaves of the plants were cleaned, dried under shade at room temperature and powdered. Dried plant materials were pulverized to fine powder and that was passed through 20 mesh size. The plant material was first defatted with petroleum ether in soxhlet and then extracted with 50% ethanol. Obtained semisolid material was filtered and filtrate was dried in rota evaporator to yield 21.63% w/w. Ethanol extract of *M. alba* leaves (EMA) was stored in desiccator for further preliminary phytochemical screening and pharmacological evaluation.

Preliminary phytochemical studies:

Extract obtained was subjected to preliminary qualitative tests for various plant constituents by suitable chemical tests [23, 24]. The amount of total phenolics was measured by standard method [25, 26]. Total phenolic contents of extracts were expressed as mg gallic acid equivalents (GAE)/g extract. All samples were analyzed in three replications.

Animals:

Wistar albino rats of either sex were obtained from animal house of the department. They were housed in an environmentally regulated room on a 12 hrs light: 12 hrs dark cycle with 25 ± 2^0C and had free access to food and water. The experimental protocol was approved by the Institutional Animal Ethical Committee of Institute and experiments were conducted according to the CPCSEA, India (CPCSEA-837/ac/2004) guidelines on the use and care of experimental animals.

Acute toxicity study:

Different doses (5, 50, 300 and 2000mg/kg, p.o.) of EMA to the animals were used for acute toxicity in accordance to Organization for Economic Cooperation Development guideline 423 [27]. Three female rats, each sequentially dosed at intervals of 48 hrs, were used for the test. Once daily cage side observations included changes in skin, fur, eyes, mucous membrane (nasal), autonomic (salivation, lacrimation, perspiration, piloerection, urinary incontinence and defecation) and central nervous system (drowsiness, gait, tremors and convulsions) changes. Mortality, if any, was determined over a period of 2 weeks**.**

Selection of doses:

For the assessment of activity, two dose level were chosen in such a way that, one dose was approximately one-tenth of the maximum dose during acute toxicity studies, and other dose, which was one-fifth of that 200, 400 mg/kg, p.o.).

Indomethacin induced ulcer:
Vehicle control, EMA in doses 200 and 400 mg/kg and ranitidine 50 mg/kg were administered orally for 7 days in their respective groups on the eighth day, experiment was performed by the standard method with some modifications as described by Gupta *et al* [28]. Briefly, wistar albino rats were fasted for 18 hrs and deprived of water for 12 hrs. Again, animals in group 1 received 1% w/v CMC solution, groups 2 and 3 were administered with EMA at the doses of 200 and 400 mg/kg, p.o., respectively, 1 hr before the indomethacin administration (20 mg/kg, p.o.). Group 4 was administered with the reference drug ranitidine (50 mg/kg, p.o.). The animals were sacrificed after 1 hr. Each stomach was then opened along the greater curvature, rinsed with normal saline and examined grossly. Ulcer index was determined using the following scoring system: 0=normal mucosa, 0.5=blushing, 1=spot ulcers, 1.5=haemorrhage streaks, 2= 3 mm <ulcers <5 mm and 2.5=ulcers>5 mm [29].

Effect of extract on liver:
The functioning of liver was assayed by evaluating the Alanine transaminase (ALT), Aspartate transaminase (AST), Alkaline phosphatise (ALP), Total protein, Albumin, Bilirubin direct and Bilirubin total.

Estimation of non-protein sulfhydryl content in stomach tissues:
All groups of rats treated were utilised to estimate the reduced glutathione (GSH) content in stomach tissues as non-protein sulfhydryls according to the method described by Sedlak *et al* [30]. Glandular segment from each stomach was homogenised in 5ml ice-cold 0.02M EDTA solution (0.02 M).

Aliquots (4 ml) of tissue homogenate were mixed with 3.2 ml of distilled water and 0.8 ml of 50% (w/v) trichloroacetic acid (50%) in glass tubes and centrifuged at 3000 rpm for 15 min, 2 ml supernatant were mixed with 4ml Tris buffer (0.4 M, pH 8.9) and 5,5'-dithio-bis(2-nitrobenzoic acid) (DTNB; 0.01 M) was added. After shaking the reaction mixture, its absorbance was measured at 412 nm within 5 min of the addition of DTNB against blank with no homogenate.

Estimation of gastric wall mucus:
Gastric wall mucus was determined according to the method of Corne *et al* [31]. The glandular segment from stomach was removed, weighed and incubated in tubes containing 1% Alcian blue solution (0.16M sucrose in 0.05M sodium acetate, pH 5.8) for 2 hrs. The Alcian blue binding extract was centrifuged and the absorbency of supernatant was measured at 498 nm. The quantity of Alcian blue extracted (µg/g of glandular tissue) was then calculated.

Histopathology study:
The samples of stomach and liver from different groups were preserved in 10% buffered formalin and processed for routine paraffin block preparation. Sections of thickness of about 5µm were cut and stained with haematoxylin and eosin.

Statistical analysis:
The results were expressed as mean±SEM and were analyzed using one-way analysis of variance followed by Dunnett's test using Graph Pad Prism 5.0 (Graph-Pad Software Inc., San Diego, California, USA). The value of $p<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION:

Preliminary phytochemical screening:
The qualitative phytochemical result shows the presence of carbohydrates, amino acids, glycosides, phenolics & tannins and, alkaloids and flavonoids

Acute toxicity study:
The EMA was found to be safe up to 2000 mg/kg with no signs of mortality or change in behavioural pattern. This result suggests that plant extract is not toxic and to be safe.

Indomethacin induced ulcer model:
Administration of indomethacin created lesions in the gastric mucosa were evident in control group and were protected in the groups pre-treated with EMA 200 mg/kg (54.32%), EMA 400 mg/kg (66.34%), or ranitidine (69.75%). Data are presented in **Table 1.**

Effect on GSH level:
Indomethacin treated rats possess decreased gastric GSH level in comparison from normal rats. The

GSH level of groups treated with EMA (400 mg/kg) were increased and are statistically significant. Groups pre-treated with EMA (400 mg/kg) were comparable to standard drug ranitidine (P<0.05). The results are presented in the **Fig.1**.

Effect on gastric wall mucus:

Indomethacin decreases gastric wall mucus. The gastric wall level in the groups treated with EMA (400 mg/kg) and ranitidine were 236.46±5.12and 239.68±4.12, respectively and also are statistically significant (P<0.05) (**Fig. 2**).

Effect of extract on liver:

Blood serum levels of Alanine transaminase (ALT) (P<0.01) were increased significantly in rats in alcohol and indomethacin induced ulcer model and that were replenish by EMA in both doses and were statistically significant (P<0.05). Other parameters, AST, ALP, total protein, albumin, bilirubin direct and bilirubin total were in normal range. The data are presented in the **Table 2**.

TABLE 1: EFFECT OF EMA ON INDOMETHACIN INDUCED ULCERATION IN RATS.

Treatment	Dose (mg/kg)	Ulcer Index (Mean ± SEM)	% Inhibition
Control	1ml	17.33 ± 1.05	-
EMA	200	7.92 ± 0.42**	54.32
EMA	400	5.83 ± 0.95 ***	66.34
Ranitidine	50	5.33 ± 0.96 ***	69.75

Values are expressed as mean±SEM (n=6). ANOVA followed by dunnet test with control group. Significance represented as **(P<0.01), *** (P<0.001).

TABLE 2: BIOCHEMICAL PARAMETERS OF RATS WITH DIFFERENT TREATMENT AGAINST INDOMETHACIN INDUCED ULCER IN RATS.

Parameters	Control	EMA (200 mg/kg)	EMA (400mg/kg)
ALT (U/L)	35.63 ± 4.12	27.42 ± 3.43*	26.45 ± 3.27*
AST (U/L)	116 ± 2.34	117 ± 3.56	115± 3.76
ALP (U/L)	130 ± 3.22	124 ± 3.24	125± 4.12
Total Protein (g/dl)	5.42 ± 0.16	5.38± 0.12	5.29 ± 0.34
Albumin (g/dl)	2.32 ± 0.04	2.24± 0.06	2.23± 0.05
Bilirubin direct (mg/dl)	0.21± 0.06	0.21± 0.05	0.19± 0.06
Bilirubin total (mg/dl)	0.46± 0.03	0.42± 0.07	0.40± 0.08

All values are expressed as mean±S.E.M., n=6. ANOVA followed by dunnet's test. * P<0.05 when the values in the groups are statistically significant against the control value.

Histopathology study: Histopathological studies (**Fig.3A-D**) further confirmedthat pre-treatment with the EMA at 400 mg/kg inhibited indomethacin induced ulcer, congestion, oedema, hemorrhage and necrosis in gastricmucosa. In reducing congestion and hemorrhage, the EMA (400 mg/kg, p.o.) efficacy was comparable to that of ranitidine.

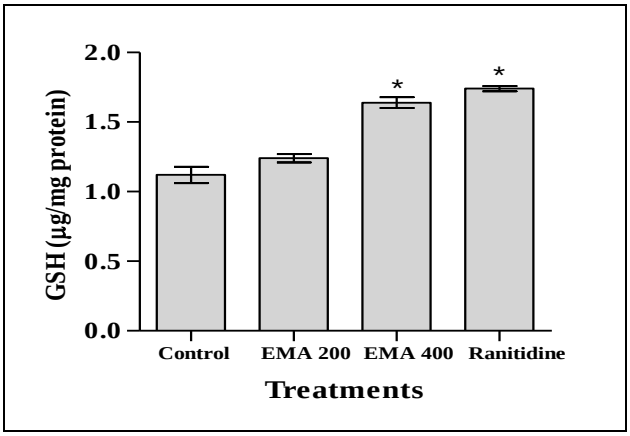

FIG. 1: GSH (µG/MG PROTEIN) LEVEL OF CONTROL, EMA (200 mg/kg), EMA (400 mg/kg) AND RANITIDINE (50 mg/kg) GIVEN ORALLY. VERTICAL BAR REPRESENT THE MEAN±SEM OF 6 ANIMALS.*=(P<0.05).

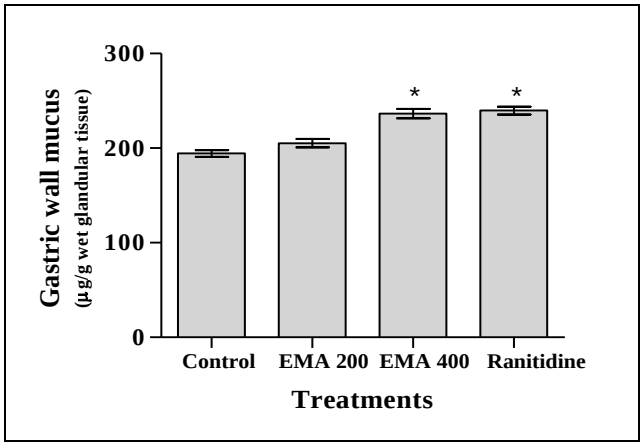

FIG.2: GASTRIC WALL MUCUS (µG/G WET GLANDULAR TISSUE) LEVEL OF CONTROL, EMA (200 mg/kg), EMA (400 mg/kg) AND RANITIDINE (50 mg/kg) GIVEN ORALLY.VERTICAL BAR REPRESENT THE MEAN±SEM OF 6 ANIMALS.*=(P<0.05).

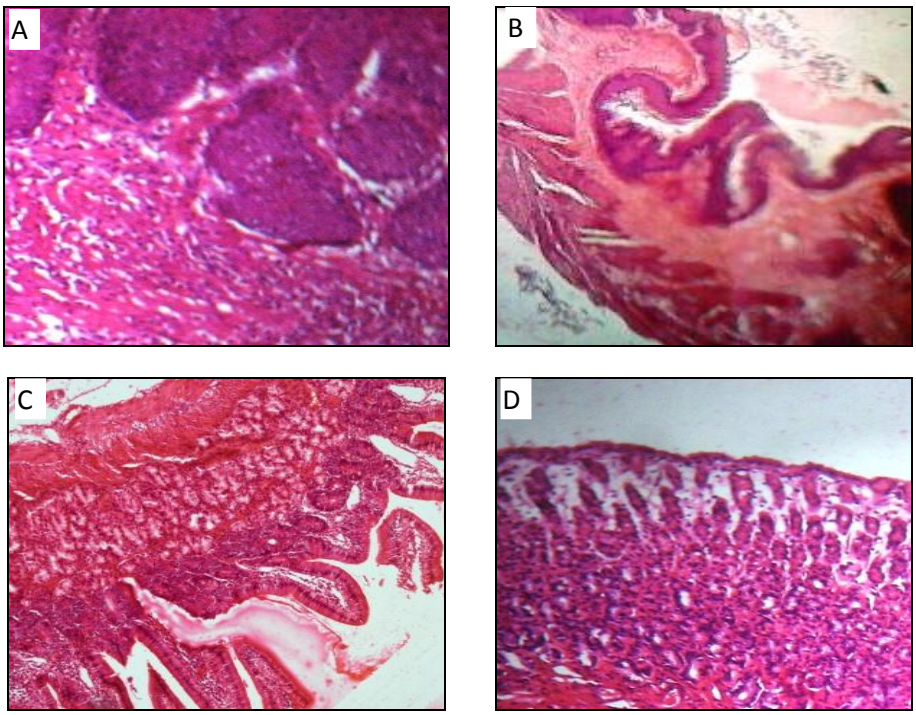

FIG.3: MICROSCOPIC OBSERVATION OF GASTRIC MUCOSA OF RAT STAINED WITH HEMATOXYLIN AND EOSIN. (A) INDOMETHACIN CONTROL; MUCOSAL LAYER IS NOT INTACT (B) EMA (100 mg/kg); MUCOSAL LAYER IS YET NOT INTACT; (C) EMA (400 mg/kg) AND (D) RANITIDINE (50 mg/kg) SHOWED INTACT MUCOSAL LAYER.

DISCUSSION: The gastric ulcer produced by indomethacin is due to the fact that this compound inhibits the synthesis of cytoprotective prostaglandins, synthesized by COX-1 and COX-2 in the stomach tissue [32]. Recently, it has been also shown that ROS possess an important role in the pathogenesis of mucosal damages caused by indomethacin, other agents besides the inhibition of COX enzymes [33]. Gastric mucus protects gastric epithelium from acid and proteases present in the luminal side of the stomach [34] and it is considered the first line of mucosal defense because it decreases physical damage to the epithelium by ingested foods. It is an important barrier against self-digestion and acts as an antioxidant, scavenging free radicals in the mucosa [35]. Ulcerogenic substances cause disruptions in this barrier and permit contact between the gastric juice and epithelial cells, leading to mucosal damage [36]. Thus, the increased stimulation of mucus production by 1.46-fold over the control group is a relevant part of the mechanism of gastric mucosal protection by EMA.

Endogenous NP-SH compounds help preserve the integrity of the mucus wall by uniting its subunits

by disulfide bridges, preventing the mucus from fetching soluble, and easily withdrawn by ulcer causing agents [37]. NP-SH compounds also prevent the production of free radicals and act as recycling antioxidants [38]. The rats that were pretreated with an inhibitor of NP-SH compounds presented ulcer areas similar to those of the vehicle-treated rats, indicating the importance of an intact NP-SH barrier to the maintenance of the EMA gastroprotective effect [39].

Protection offered by the EMA against indomethacin-induced gastric ulceration may be linked to their advantageous medicinal attributes occasioned by secondary metabolites. These include ability to scavenge free radicals and regulate mucosal membrane permeability thereby countering the effect of indomethacin on gastric acid secretion. This is in agreement with the scientific community, where gastroprotective potentials of plant extracts against indomethacin-ulcerated rats were associated with their secondary metabolite [40, 41].

CONCLUSIONS: In conclusion, it appears that *Morus alba* L. possess gastroprotective principles which protect against gastric mucosal damage induced by indomethacin. Probably these effects are due, partly at least, to the presence of flavonoids, glycosides phenolics and tannins in the ethanol extract of the *Morus alba* leaves. The biochemical parameters also suggest the normal functioning of the liver.

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