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# Effect of Leukotriene Receptor Antagonist Montelukast Along with Curcumin against Gastric Ulceration

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**ABSTRACT**
*Curcumin*, a yellow pigment in the spice turmeric, has been used for centuries as a treatment for inflammatory diseases. This yellow pigment has anti-secretary property in different experimental ulcer models. Montelukast, a leukotriene receptor antagonist has been used for the treatment of inflammatory disease. This substance has antioxidant property in different experimental models. This data supports to evaluate the synergistic effect of Montelukast along with Curcumin against gastric ulceration. Gastric ulcers were induced by administering Aspirin (200 mg/kg) plus pylorus ligation and Indomethacin (20 mg/kg). Evaluation of Montelukast along with Curcumin was carried out in above experimental models. All the Montelukast (10 mg/kg) along with *Curcumin* (60 mg/kg) treated animals showed more significant reduction of ulcer index in both above experimental models compared to individual treatment with both, *Curcumin* and Montelukast.

**Keywords:** Gastric ulcer, Montelukast, Curcumin, Pylorus ligation, Ulcer index.

## INTRODUCTION

Peptic ulcer occurs in that part of the gastrointestinal tract which is exposed to gastric acid and pepsin, i.e., the stomach and duodenum. It results probably due to an imbalance between the aggressive (acid, pepsin) and the defensive (gastric mucus and bicarbonate secretion, prostaglandins, nitric oxide, innate resistant of the mucosal cells) factors. [1] There are two types of peptic ulcer problems in humans: Acute peptic ulcers may arise suddenly in the digestive tract. Their pains are much more severe and are immediately felt whenever any spicy or gassy food is eaten. These types of ulcers usually cause nausea and vomiting. Chronic ulcer is a long lasting condition, which cannot be treated easily. They cause continuous pain whenever any type of food is eaten. Burning sensation is common, leading to nausea and vomiting. [2] The goals of treating peptic ulcer disease are to relieve pain, heal the ulcer and prevent ulcer recurrence. Currently, efforts are on research of a suitable treatment from natural product sources. A large number of species and herbs have been evaluated by various researchers for their anti-ulcer effects to achieve a favourable outcome. [3] *Curcuma longa*, an indigenous plant, widely grown in India, is known to be effective in the treatment of gastro-intestinal disorders. Fresh extract of *C. longa* is used as anti-ulcer agent and was found to afford almost complete protection against gastric ulcers. Research has demonstrated anti-inflammatory, antioxidant, and antacid properties of Curcumin. [4-5] Montelukast is a new anti-inflammatory drug that interferes directly with leukotriene production (5-lipoxygenase inhibitors) and/or reception (leukotriene receptor antagonists). It was reported that leukotriene receptor $LTC_4/LTD_4$ antagonists ameliorate the ethanol and Indomethacin induced gastric mucosal damage. Also the gastro protective effect of Montelukast is related to its antioxidant effects. [6] Treatment with Montelukast causes some adverse effects such as cough, dizziness, headache, indigestion, nausea, tiredness, trouble sleeping, weakness, rashes, itching, aggressive behavior, agitation, dark urine, fever, hallucinations, and yellowing of the skin or eyes. [7] Because of these adverse effects of Montelukast, its combination with herbal drug may be more safe and effective. This prompted to evaluate the effect of Montelukast along with *Curcumin* against gastric ulceration. The aim of the study was to study the effect of leukotriene receptor antagonist and *Curcumin* against gastric ulceration and to identify the probable mechanism for the synergistic action in combination.

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## MATERIALS AND METHODS

### Drugs and chemicals

*Curcumin* extract was collected form Himedia chem, Mumbai. Montelukast was collected from Torrent pharmaceuticals Ltd, Ahmedabad. All other chemicals used

such as Aspirin, Indomethacin, tween 80, sodium chloride, phenolphthalein, etc were purchased from Karnataka fine chem-Bangalore, Loba chemie-Mumbai, Merck-Mumbai.

Doses of 60 mg/kg of *Curcumin* extract and 10 mg/kg of Montelukast were prepared as a solution and 0.1% Tween 80 solution was used as vehicle control. All the treatments were administered orally and were freshly prepared just before dosing.

Wistar albino rats (180 to 200 g) of either sex procured from Indian Institute of Sciences were used for this study. They were maintained under standard conditions (temperature 22 ± 2$^{o}$C, relative humidity 60±5% and 12 h light/dark cycle). The animals were housed in sanitized polypropylene cages containing sterile paddy husk as bedding. They were having free access to standard pellet diet and water *ad libitum*. The Institutional Animal Ethics Committee approved the experimental protocol. All the animals received humane 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".

**Aspirin plus pylorus ligation induced ulcer**

Wistar rats were randomly divided into 5 groups of 6 each.

Group I: Vehicle control (0.1% Tween 80) p.o

Group II: Positive control, Aspirin (200 mg/kg) p.o

Group III: Aspirin (200 mg/kg) + Curcumin extract (60 mg/kg) p.o

Group IV: Aspirin (200 mg/kg) + Montelukast (10 mg/kg) p.o

Group V: Aspirin (200 mg/kg) + Curcumin extract (60 mg/kg) + Montelukast (10 mg/kg) p.o

The ulcers were induced from group II to group V by oral administration of Aspirin for 3 days and pylorus was ligated on the fourth day. The animals were fasted for 36 hours before pylorus ligation but had free access to water. After 36 hours of fasting, under light ether anesthesia, Pylorus ligation was done without causing any damage to the blood supply of the stomach. Four hours after the pyloric ligation, the animals were sacrificed by decapitation. The stomachs were removed, opened along with greater curvature, fixed on a cork plate and the number and severity of ulcers was registered using the following scores and the ulcer index was determined. [8-11]

- 0 = no ulcer
- 1 = superficial ulcers
- 2 = deep ulcers
- 3 = perforation

Ulcer index was calculated using the formula:

$$UI = UN + US + UP \times 10^{-1}$$

- *U*N= average of number of ulcers per animal
- *U*S = average of severity score
- *U*P = percentage of animals with ulcers

The gastric contents were centrifuged at 3000 rpm for 10 minutes. Volume was noted. 1 ml of supernatant was pippetted out and dilute to 10 ml with distilled water. Acidity was determined by titration with 0.1 N NaOH using phenolphthalein indicator. [12]

Acidity was calculated by using the formula:

$$\text{Acidity} = \frac{\text{Volume of NaOH} \times \text{Normality of NaOH} \times 100\ \text{mEq/litre}}{0.1}$$

**Indomethacin induced ulcer**

Wistar rats were randomly divided into 5 groups of 6 each.

Group I: Vehicle control (0.1% Tween 80) p.o

Group II: Positive control, Indomethacin (20 mg/kg) p.o

Group III: Indomethacin (20 mg/kg) + Curcumin extract (60 mg/kg) p.o

Group IV: Indomethacin (20 mg/kg) + Montelukast (10 mg/kg) p.o

Group V: Indomethacin (20 mg/kg) + Curcumin extract (60 mg/kg) + Montelukast (10 mg/kg) p.o

The ulcers were induced from group II to group V by oral administration of Indomethacin. The group I was served as normal control. The rats were fasted for 24 hours prior to the experiment. All the drug solutions were given 10 minutes prior to Indomethacin administration. After 6 hours, rats were sacrificed by decapitation, stomachs were removed and 2% v/v formalin-saline solution injected into totally ligated stomach for overnight storage. The next day, stomachs were opened along with greater curvature, washed with warmed water, and the ulcers index was measured as above method. [8-9, 13]

**STATISTICAL ANALYSIS**

All data will be expressed as mean ± SEM. The statistical significance between groups will be compared using one way ANOVA, followed by Dunnet's t-test (multiple comparisons). $P < 0.05$ will be considered as significant.

**RESULTS**

The mean ulcer index and total acidity in Aspirin plus pylorus ligation are presented in Fig. 1 and 2. In Aspirin plus pylorus ligation induced gastric ulcer, Montelukast (10 mg/kg) co-administered along with Curcumin (60 mg/kg) showed more significant ($P < 0.0001$) reduction in ulcer score and total acidity when compared to individual administration of both.

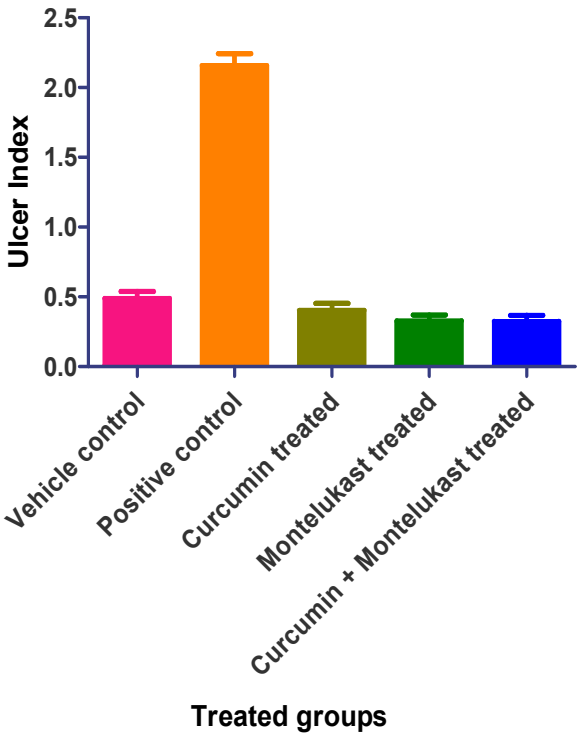


**Fig. 1: Ulcer Index of Aspirin plus pylorus ligation induced ulcer**

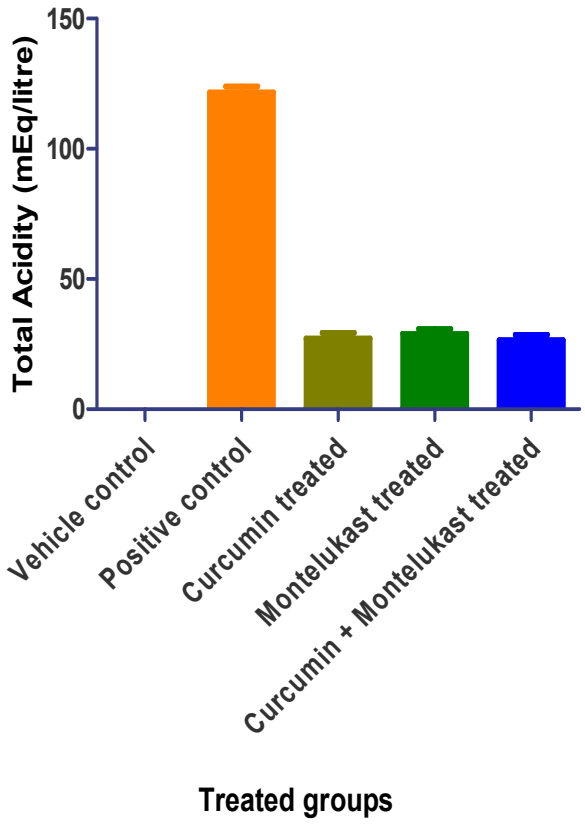


**Fig. 2: Total Acidity in Aspirin plus pylorus ligation induced ulcer**

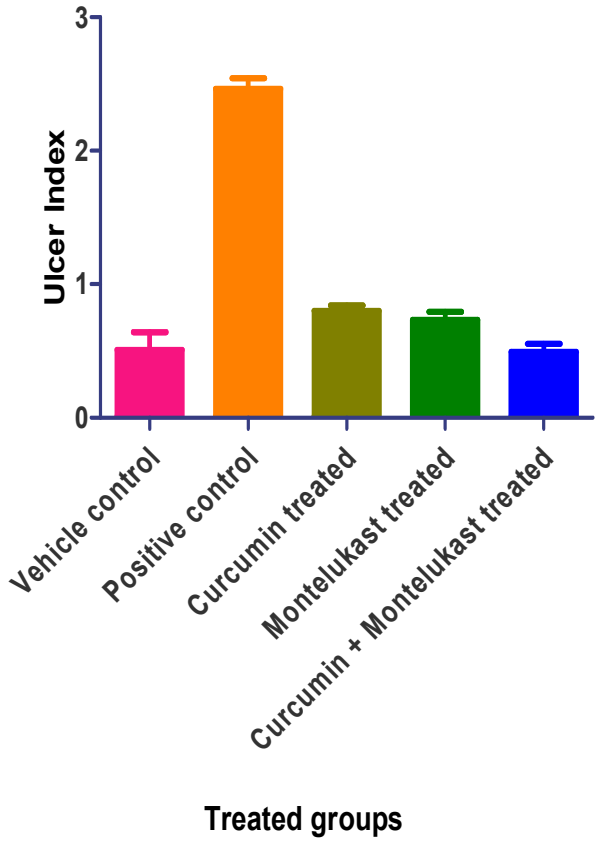


**Fig. 3: Ulcer Index of Indomethacin induced ulcer**

The mean ulcer index in Indomethacin induced ulcer is presented in Fig. 3. Individual administration of both *Curcumin* and Montelukast significantly reduced ulcerogenic activity when compared to positive control group. The effect was still more significant when Montelukast co-administered along with Curcumin when compared to positive control group.

## DISCUSSION

Aspirin plus pylorus ligation aggravated the acid secretion, which in turn caused increase in gastric volume, increased free and total acidity and low pH. Ulcers are induced due to increase in offensive factors like gastric acid, pepsin and bile salts but it has been observed that gastric ulcer patients have either normal or below normal acid level in the stomach. This indicates that other mechanisms are also involved in ulcer formation. Moreover the disturbance of defensive factors like mucus secretion, bicarbonate secretion and mucosal blood flow has been reported to cause ulcers. Therefore, it is an ideal model to evaluate the efficacy of a drug against gastric ulceration. [12]

Both *Curcumin* extract and Montelukast inhibited ulcerogenic activity of pylorus ligation significantly. Both *Curcumin* (60 mg/kg) and Montelukast (10 mg/kg) were reduced ulcer index and total acidity significantly. Co-administration of Curcumin along with Montelukast found still more significant. The reason for their synergistic activity may be due to flavonoids and antioxidant properties which are the major mechanism responsible for anti-ulcer activity.

Nonsteroidal anti-inflammatory agents, like Indomethacin and acetyl-salicylic acid induce gastric lesions in man and in experimental animals by inhibition of gastric cyclo-oxygenase resulting in less formation of endogenous prostaglandin, the predominant prostanoid produced in the gastric mucosa. Indomethacin also inhibits gastro duodenal bicarbonate secretion as well as gastric mucosal blood flow. The model shows drug's effect on cytoprotection and gastric acid secretion. [14]

There was significant decrease in ulcer index in *Curcumin* extract and Montelukast treated animals compared to Indomethacin treated positive control animals. Combination of Montelukast along with *Curcumin* had shown better significant activity than individual treatment.

In both the ulcerogenic models, the combination of Montelukast and *Curcumin* extract was found to be more effective than individual treatment. Curcumin found to be antisecretory and cytoprotective in nature. Montelukast showed its ulcer protective action by preventing mucosal injury and the antioxidant property. The mechanism of actions of *Curcumin* extract and Montelukast are complementary to each other in ulcer preventive action, hence the potentiating activity.

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