

## Investigation Of Anti-Ulcer Activities By Using Indomethacine Induced & Cold-Water Restraint Procedure In Experimental Rat: Meta Analysis

**Dr. KESHAMMA E<sup>1</sup>, TUSHAR SINGHAL<sup>2</sup>, PURABI SAHA<sup>3</sup>, DEVINDER KUMAR<sup>4</sup>, AJAY KUMAR<sup>5\*</sup>, ANURAG CHOURASIA<sup>6</sup>, ROSHAN KUMAR<sup>7</sup>**

<sup>1</sup>Associate Professor, Department of Biochemistry, Maharani Cluster University, Palace road, Bangalore-560001, INDIA.

<sup>2</sup>Senior Clinical Researcher, Department of Clinical Research, MAX Healthcare Dehradun, Uttarakhand, INDIA.

<sup>3</sup>Department of Pharmacy, Uttaranchal Institute of Pharmaceutical Sciences, Uttaranchal University, Dehradun-248007, Uttarakhand, INDIA.

<sup>4</sup>Asst. Professor, Dept. of Pharmacology, Amar Shaheed Baba Ajit Singh Jujhar Singh Memorial College of Pharmacy, Bela, Punjab, INDIA.

<sup>5</sup>Department of Zoology, Kumaun University, Nanital-263002, Uttarakhand, INDIA.

<sup>6</sup>Assistant Professor, Ramanand Institute of Pharmacy and Management, Haridwar, INDIA.

<sup>7</sup>Department of Pharmacology, Dev Bhoomi Institute of Pharmacy and Research, Dehradun-248007, Uttarakhand, INDIA.

Corresponding Author\*\*ROSHAN KUMAR

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### Abstract

Medicinal plants have long been known to be healing. Most societies have used herbs for thousands of years. The increasing use of herbal treatments and healthcare preparations is linked to the discovery of natural items with medicinal properties. The herbal medicines of preliterate societies continue to astound us with their extensive green pharmacy. Herbal healing knowledge was passed down orally from healer to healer. Dietary and lifestyle changes can help reduce the risk of stomach ulcers. Larger than 5- millimeter cracks in stomach mucosal barrier permeate muscularis mucosa. It is crucial to recognize that this sickness is both preventable and treated. The treatment for stomach ulcers varies depending on the etiology. The stomach membrane is easily and quickly penetrated by cold water, so this study compared mixture and omeprazole to see which had better anti-ulcer and antioxidant benefits in a rat ulcer and oxidative stress model induced by cold water immersion. Acidity of gastric juice was determined by using pH meter apparatus. Then separated and measured volume by graduated cylinder. The stomachs of the sacrificed rats were taken and immersed in 10% formalin solution and stained with hematoxylin and eosin stain for examination.

**Keywords:** Herbal Plant, Ulcer, Cold water, Indomethacin, gastric juice.

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## Introduction

Plants, animals, microbes, minerals, and marine life have all served as sources of food and medicine throughout history. No matter the culture or time period, the ideas and techniques of treating illness are universal. Medicinal plants have long been known to be healing. Most societies have used herbs for thousands of years<sup>1</sup>. The increasing use of herbal treatments and healthcare preparations is linked to the discovery of natural items with medicinal properties. The herbal medicines of preliterate societies continue to astound us with their extensive green pharmacy. Herbal healing knowledge was passed down orally from healer to healer. Dietary and lifestyle changes can help reduce the risk of stomach ulcers. Larger than 5- millimeter cracks in stomach mucosal barrier permeate muscularis mucosa<sup>2</sup>. It is crucial to recognize that this sickness is both preventable and treated. The treatment for stomach ulcers varies depending on the etiology. The body's inherent defense mechanisms protect the stomach mucosa from the acidic gastric lumen<sup>3,4</sup>. This can cause alterations in the stomach mucosa, resulting in erosion and ulcers. The presence of prostaglandins and mucus helps to keep the stomach mucosa healthy. Non-steroidal anti-inflammatory drugs (NSAIDs), hypoxia, alcohol, and *Helicobacter pylori* infection are all known to impair this barrier. The most common cause of stomach ulcers is *Helicobacter pylori* (*H. pylori*) infection, however NSAIDs can also cause gastric prostaglandin loss. Less common causes of hyper gastric include gastric outlet obstruction, cancer, smoking, and Crohn's disease (Zollinger-Ellison syndrome)<sup>5-9</sup>. Other reasons include CMV, chemotherapy, and radiation. All of these factors cause the mucosal barrier to dissolve, exposing the stomach mucosa to toxic stomach acids. Peptic ulcers more typically afflict younger to older adults, but can be identified in young adults. A few days to months into the disease's active phase, they may go away on their own or require medicine<sup>10</sup>. It also affects due to *H. pylori* infections. Person may have gastrointestinal difficulties if you suffer stomach cramps and nausea. If these symptoms don't go away, you may have a peptic ulcer. About stomach ulcers, A peptic ulcer is a lining irregularity in the stomach or the first segment of the small intestine, the duodenum. When it affects your stomach, it's called a gastric ulcer<sup>11-14</sup>. A duodenal ulcer is a hole in the duodenum's lining. Stomach's powerful acid breaks down and digests your meals. Anything that comes into contact with a strong acid will perish. That's why your stomach and intestines have special linings to protect them from bacteria. If this lining is weakened, acids An acid burns a hole in the wall of the stomach or duodenum, requiring rapid medical intervention. It's debatable whether your boss is causing your ulcer, while stress may be a factor. Your ulcer is most likely caused by *H. pylori*, a stomach bug. Other ulcer risk factors include smoking, excessive alcohol consumption, and frequent use of Nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin and ibuprofen. Small ulcers may go unnoticed due to lack of symptoms. Larger ulcers can cause abdominal pain, nausea, and a feeling of fullness. One way is an upper endoscopy, which involves inserting a thin tube with a camera into the stomach and small intestine<sup>15</sup>. X-rays are taken after consuming a radioactive substance called barium to estimate your lower GI, to treat *H. pylori* infections, a specific medication regimen is required. Proton pump inhibitors (PPIs) as Prilosec or prevacid help reduce stomach acid. If having *H. pylori*, NSAIDs consumption should be avoided for a for a long time. Instead, Tylenol. If consuming NSAIDs, a person should also take an acid-blocking drug to

prevents sensitive stomach.

## **MATERIAL&METHODS**

We search from different web source like Scopus, web of science, pubmed, publon, mdpi etc. Keywords: Croton macrostachyus Hocsht & Daucus carota, Omeprazole, Indomethacin, Anti-ulcer activity.

**Table.1: Drugs used**

Drugs used	Manufacturer
Omeprazole	Wings biotech Pvt. Ltd. (Himachal Pradesh)
Indomethacin	Shaklak's Pharmaceuticals Pvt. Ltd

## **Phyto-Chemical Screening**

Using crude drug combinations, alkaloids, saponins, carbohydrates, tannins, flavonoids, steroids, and triterpenoids substances were detected in Croton macrostachyus Hocsht and Daucus carota using standard protocols.

## **Determination of Alkaloids**

HCl was used to dilute and filter small quantities of crude drug combination (about 50mg). The filtrate was tested using alkaloidal reagents.

### **Mayer's test**

In the test tube, added 2-3 drops of Mayer's reagent to few ml of aqueous mixture of crude drugs. The development of white precipitates showed the presence of alkaloids.

### **Dragendorff's test**

In the test tube, added 2-3 drops of Dragendorff's reagent to a few ml of aqueous mixture of crude drugs. The appearance of orange reddish brown precipitates indicated the presence of alkaloids.

### **Wagner's test**

In the test tube, added 2-3 drops of Wagner's reagent to few ml of aqueous mixture of crude drugs. The appearance of reddish-brown precipitates indicated the presence of alkaloids.

### **Hager's test**

In the test tube, added 2-3 drops of Hager's reagent to few ml of aqueous mixture of crude drugs. The appearance of yellow color precipitates indicated the presence of alkaloids.

### **Determination of Glycosides**

Glycosides were detected in 50 mg of crude drug mixtures after two hours of hydrolysis in strong hydrochloric acid on a water bath, followed by filtration.

#### **Borntrager's test**

After the hydrolysate had been filtered and the chloroform layer had been separated, an ammonia solution (10% ammonia) was added to the chloroform layer. The color of the glycosides was used to identify them.

#### **Legal's test**

30 mg of the crude drug mixture, which was dissolved in a few ml of Pyridine, was alkalized with 10% sodium hydroxide, and the pink hue of glycoside indicates its presence.

### **Determination of Carbohydrates**

Crude drug mixture (100 mg) was mixed with water, the solution is filtered out via a fine mesh strainer. The filtrate was then put through a series of tests.

#### **Molisch's test**

Crude drug filtrates were mixed with 2 drops of alcoholic solution of  $\alpha$ -naphthol and 1 mL of strong sulphuric acid, which was gently poured to the test tube and later stand for about an hour. Carbohydrates were indicated by a violet ring.

#### **Fehling's test**

Fehling solutions A and B heated with one ml of aqueous mixture of crude drug in a water bath. The presence of sugar was indicated by the appearance of a crimson precipitate.

#### **Barfoed's test**

In the test tube, 2-3 drops of Barfoed's reagent were added to few ml of aqueous mixture of crude drugs, and the solution was then heated in boiling water for three minutes. The appearance of red precipitate indicated the presence of sugar.

### **Determination of Saponins**

Distilled water was used to dilute the crude drug mixture (50mg) to make a final solution of 20ml, for fifteen minutes, the suspension is shaken vigorously in a graduated cylinder. Saponins were detected by a foam layer of two centimeters

### **Determination of Phenolic and Tannin Compounds**

#### **Ferric chloride Test**

In 5 ml pure water, the crude drug mixture (50 mg) was dissolved. Few drops of a neutral 5% ferric chloride solution were added to mixture. The appearance of dark green color indicated the presence of phenolic compounds.

#### **Gelatin-Test**

Two ml of 1% gelatin solution with 10% sodium chloride was added to the crude drug mixture (50mg). The presence of phenolic compounds was indicated by the appearance of white precipitate.

#### **Lead Acetate Test**

3 ml of 10 % lead acetate solution was added to 50 mg of crude drug mixture, which was dissolved in purified water. The presence of phenolic compounds was indicated by a large white precipitate in the sample.

#### **Antiulcer activity & (drugs and dosing)**

##### **Cold water immersion induced model (Acute model)**

Albino wistar rats were divided in 4 groups of 4-6 months of age, 200-250gm. 6 albino wistar rats in each group.

Group I-Control group-treated with vehicle (normal saline) alone, p.o.

Group II-Standard drug omeprazole (25mg/kg), i.p.

Group III-Mixture of Croton macrostachyus Hocsht (100mg/kg) and Daucus carota (100mg/kg) in 0.1% tween80, taken in 1:1, given p.o.

Group IV- Mixture of Croton macrostachyus Hocsht 200mg/kg) and Daucus carota (200mg/kg) in 0.1% tween80, taken in 1:1, given p.o.

##### **Indomethacin induced ulcer model (Chronic model)**

Albino wistar rats were divided in 4 groups of 4-6 months of age, 200-250gm. 6 albino wistar rats in each group.

Group I-Control group-treated with vehicle (normal saline) alone, p.o.

Group II-Standard drug- omeprazole 25mg/kg i.p.

Group III-Mixture of Croton macrostachyus Hocsht (100mg/kg) and Daucus carota (100mg/kg) 0.1% tween80, taken in 1:1, given p.o.+ indomethacin (30mg/kg) i.p.

Group IV- Mixture of Croton macrostachyus Hocsht 200mg/kg) and Daucus carota (200mg/kg) (30mg/kg) i.p.

## Result & Discussion

**Table.2:Phyto-chemical study of Croton macrostachyus Hocsht**

Types of constituents	Distilled Water	Petroleum Ether	Chloroform	Methanol	Ethyl Acetate	Benzene
Carbohydrates	+++	+++	++	+++	-	-
Flavonoids	---	+	++	+++	-	-
Saponins	++++	--	--	++	-	+
Glycosides	+++	-	+	++	++	+
Alkaloids	-	++	++	++	+	+
Triterpenoids	-	+++	++	+++	++	++
Tannins & Phenolics	+	++	+	+++	++	+

Keywords:(+) shows the presence shows the moderate presence (+++) shows the intense presence and, (-) shows absence

**Table 3:Phyto-chemical study of Daucus carota**

Type of Constituents	Distilled water	Petroleum ether	Chloroform	Methanol	Ethyl acetate	Benzene
Carbohydrates	+	++	+++	+++	-	++
	+					
	+					
Flavonoids		-	+++	++	-	+++
Saponins	+	+	++	+++	-	+++

Glycosides	-	-	-	+++	-	-
Alkaloids	-	-	-	-	+++	-
Triterpenoids	-	-	-	+++	-	-
Tannins and Phenolic	-	+++	-	+++	-	-

#### Cold water immersion stress ulcer model

Immersion in cold water for 18 hours upto process resulted gastric lesion in rats. The stomach membrane is easily and quickly penetrated by cold water, so this study compared Croton macrostachyus Hocsht, Daucus carota mixture and omeprazole to see which had better anti-ulcer and antioxidant benefits in a rat ulcer and oxidative stress model induced by cold water immersion<sup>16-23</sup>. The results of this study showed changes in the ulcer length of test group rats at both the doses of Croton macrostachyus Hocsht and Daucus carota 200mg/kg body weight ( $4.50 \pm 0.16$ ) and 400mg/kg body weight ( $3.60 \pm 0.25$ ) in comparison to control group rats ( $7.90 \pm 0.40$ ) which was comparable to standard group ( $2.60 \pm 0.85$ ). For pH of gastric juice in the control group very low pH was observed ( $5.70 \pm 0.82$ ) in the test groups the pH was high at both the doses of Croton macrostachyus Hocsht and Daucus carota 200mg and 400mg/kg body weight ( $6.60 \pm 0.31$ ), ( $7.50 \pm 0.36$ ) which was comparable to standard group ( $7.58 \pm 0.54$ ). Present studies showed changes in the volume of gastric juice of test group at both the doses of Croton macrostachyus Hocsht and Daucus carota 200mg/kg body weight ( $4.30 \pm 0.38$ ) and 400mg/kg body weight ( $2.00 \pm 0.65$ ) in comparison to control group rats ( $4.67 \pm 0.54$ ) which was comparable to standard group ( $2.80 \pm 0.18$ ) as shown in table 9 respectively. The rats treated with Croton macrostachyus Hocsht and Daucus carota decreased the intensity of gastric mucosal damage induced by cold water immersion. The % protection of gastric lesion was more than (79.63%) in the groups of animals received Croton macrostachyus Hocsht and Daucus carota 400 mg/kg when compare to and 200mg/kg.

**Table: 4 Effect of cold-water immersion stress ulcer model**

Groups	Number of Animals (n)	Ulcer length in (mm)	pH of gastric juice	Volume of gastric juice in (cm <sup>3</sup> )
Control group	6	$7.90 \pm 0.40^*$	$5.70 \pm 0.82$	$4.67 \pm 0.54$

Standard group (omeprazole)	6	$2.60 \pm 0.85$	$7.58 \pm 0.54^{***}$	$2.80 \pm 0.18^{***}$
Croton macrostachyus Hocsht and Daucus carota(200mg/kg) b. w	6	$4.50 \pm 0.16$	$6.60 \pm 0.31^{**}$	$4.30 \pm 0.38$
Croton macrostachyus Hocsht and Daucus carota(400mg/kg) b. w	6	$3.60 \pm 0.25^{**}$	$7.50 \pm 0.36$	$2.00 \pm 0.65^{**}$

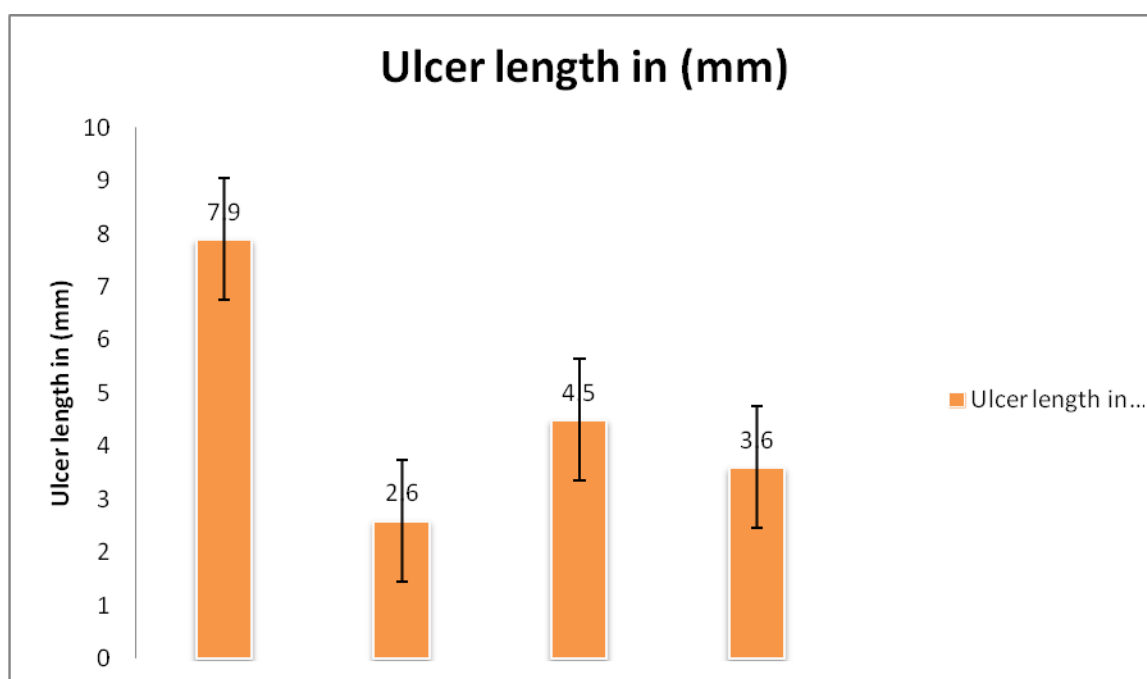
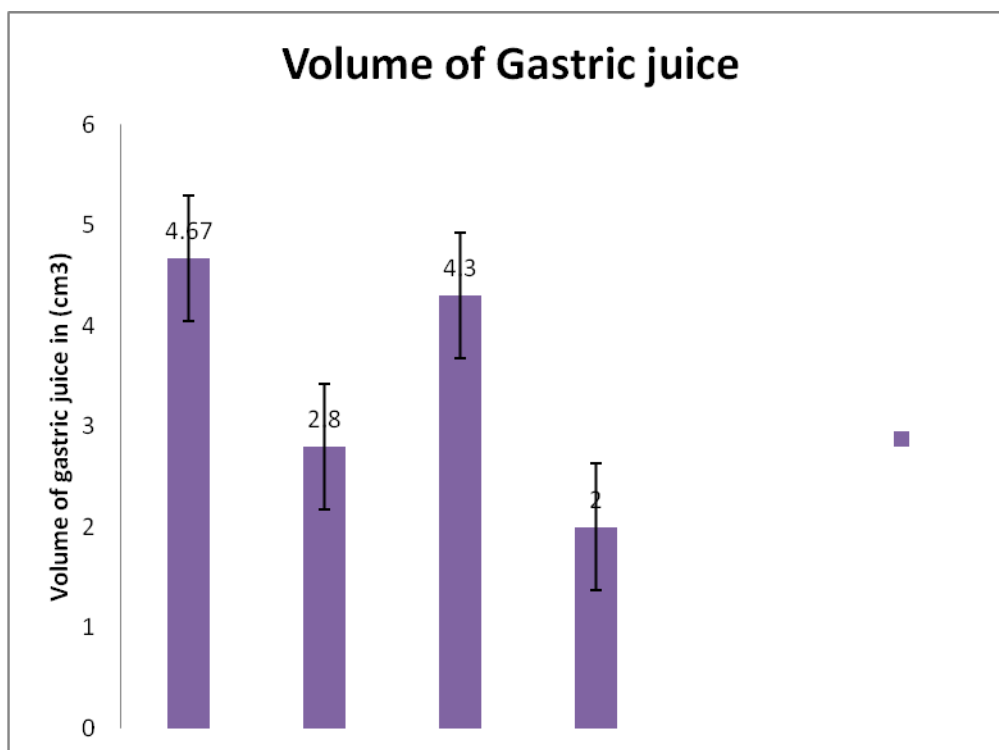


Fig.1: Effect of Croton macrostachyus Hocsht and Daucus carotaon gastric ulcer length in cold water immersion stress ulcer model





**Fig.2:**Effect of *Croton macrostachyus* Hocsht and *Daucus carota* on pH of gastric juice in cold water immersion stress ulcer model



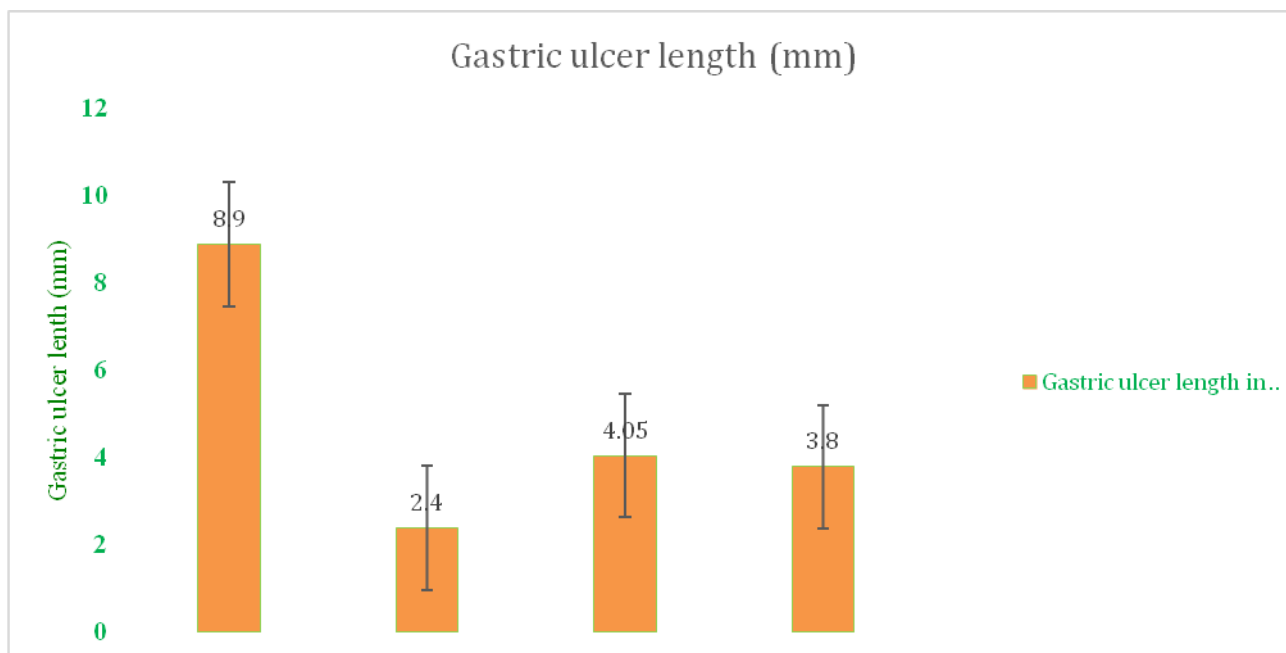
**Fig.3:** Effect of *Croton macrostachyus* Hocsht and *Daucus carota* on volume of gastric juice in cold water immersion stress ulcer model

Indomethacin induced ulcer model

Administration of indomethacin resulted in the production of gastric lesions mainly in the glandular portion of the stomach. The result of this study showed changes in the ulcer length of test group rats at both the doses of Croton macrostachyus Hocsht and Daucus carota 200mg/kg body weight ( $4.05 \pm 0.61$ ) and 400mg/kg body weight ( $3.80 \pm 0.21$ ) in comparison to control group rats ( $8.90 \pm 0.50$ ) which was comparable to standard group ( $2.40 \pm 0.78$ ) as shown in table 14 respectively. For pH of gastric juice in the control group very low pH was observed ( $4.70 \pm 0.28$ ) in the test groups the pH was high at both the doses of Croton macrostachyus Hocsht and Daucus carota 200mg and 400mg/kg body weight ( $6.60 \pm 0.81$ ), ( $7.60 \pm 0.42$ ), as compared to standard group ( $8.58 \pm 0.54$ ) as shown in table 15 respectively. Present study showed changes in the volume of gastric juice of test group at both the doses of Croton macrostachyus Hocsht and Daucus carota 200mg/kg body weight ( $3.05 \pm 0.38$ ) and 400mg/kg body weight ( $2.00 \pm 0.19$ ) in comparison to control group rats ( $5.58 \pm 0.45$ ), as compared to standard group ( $1.60 \pm 0.18$ ) as shown in table 16 respectively. The rats treated with Croton macrostachyus Hocsht and Daucus carota decreased the intensity of gastric mucosal damage induced by indomethacin. The % protection of gastric lesion was more (69.63%) in the groups of animals received Croton macrostachyus Hocsht and Daucus carota 400 mg/kg when compare to and 200mg/kg.

**Table.5: Effect of indomethacin induced ulcer model**

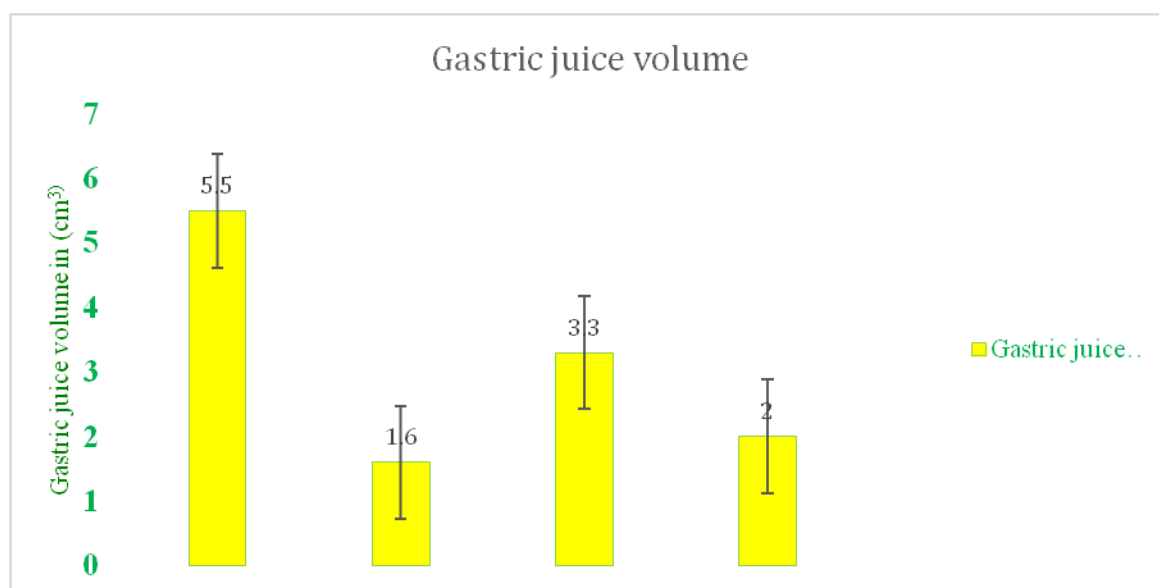
Groups	Number of Animals (n)	Ulcer length in (mm)	pH of gastric juice	Volume of gastric juice in (Cm <sup>3</sup> )
Control group	6	$8.90 \pm 0.50^*$	$4.70 \pm 0.28$	$5.58 \pm 0.45$
Standard group (omeprazole)	6	$2.40 \pm 0.78^*$	$8.58 \pm 0.54$	$1.60 \pm 0.18$
Croton macrostachyus Hocsht and Daucus carota (200mg/kg) body weight	6	$4.05 \pm 0.61$	$6.60 \pm 0.81^{***}$	$3.30 \pm 0.38$
Croton macrostachyus Hocsht and Daucus carota (400mg/kg) body weight	6	$3.80 \pm 0.21^*$	$7.60 \pm 0.42$	$2.00 \pm 0.19$



**Fig.4: Effect of Croton macrostachyus Hocsht and Daucus carota on gastric ulcer length in indomethacin induced ulcer model**



**Fig.5: Effect of Croton macrostachyus Hocsht and Daucus carotaon pH of gastric juice in indomethacin induced ulcer model**



**Fig.6 Effect of Croton macrostachyus Hocsht and Daucus carotaon gastric juice volume in indomethacin induced ulcer model**

## Conclusion

On both people and animals, *Croton macrostachyus* Hocsht and *Daucus carota* has a variety of biological, biochemical, and physiological effects. According to the present study the experimental models chosen were indomethacin induced ulcers and cold-water immersion stress model, caused ulcer development by depleting cyto-protective PGs. The cellular integrity and production of mucus in the gastric and duodenal mucosa are maintained by PGE<sub>2</sub> and PGI<sub>2</sub>. The current study discovered that the crude drug combination of *Croton macrostachyus* Hocsht and *Daucus carota* powder has greater anti-ulcer and antioxidant efficacy than the commercially available antiulcer drug omeprazole. According to phytochemical screening tri-terpenes and flavonoids may be responsible for their anti-oxidant capacity, as well as for enhancing antioxidant status and mucus production. The protective effect on the treatment of gastric ulcers may be due to these factors. The suggested unprocessed drug combination might be a suitable candidate for carrying further clinical trials on ulcer patients.

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