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ORIGINAL ARTICLE



# Experimental evaluation of anti-ulcer potential of Nigella sativa oil in gastric ulcers in Albino rats

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## Abstract

**Introduction and Objective.** Peptic ulcer is a gastrointestinal disease that is characterized by mucosal damage. Nigella sativa (NS) is a medicinal plant increasingly used in practice for treating gastrointestinal diseases. The aim of the study was to evaluate the antiulcer potential of Nigella sativa oil in Albino rats.

**Materials and method.** The study utilized two methods of gastric ulcer induction in Albino rats. The Aspirin-induced gastric ulcer method consisted of 3 groups, with 6 rats in each group, which received pre-treatment once a day orally for 5 days. Group-1 (Control) animals received distilled water. Group-2 (Standard) animals received the standard drug, Ranitidine. Group-3 (Expermintal) animals received the test drug – Nigella sativa oil. The forced swim induced acute gastric ulceration method consisted of 3 groups i.e., control, standard, and test group with 6 rats in each group. After 5 days of respective pre-treatment, the animals were subject to a forced swim test. On day 7, 4 hours after Aspirin ingestion, the animals were sacrificed by stunning. The stomachs of the sacrificed animals was dissected for ulcer scoring.

**Results.** In the Aspirin-induced ulcer method, the percentage protection from ulcer formation was 47.5% in the Nigella sativa group and 52.9% in the standard group. The effect of Nigella sativa oil in comparison to control was statistically significant (p value=0.03). In the forced swim induced acute gastric ulceration method, the percentage protection offered by Nigella sativa oil was 73%, whereas it was 69.6% in the Ranitidine group, and the effect of Nigella sativa oil in comparison to the effect of control was statistically significant (p value=0.03).

**Conclusions.** The study demonstrated that NS oil has significant anti-ulcer potential in rats, which is comparable to the standard drug.

## Key words

anti-ulcer, *Nigella sativa* oil, Aspirin-induced gastric ulcer, forced swim-induced gastric ulcer

## INTRODUCTION

Peptic ulcer is a common disease of the 19th and 20th centuries. The estimated prevalence of peptic ulcer disease in the general population is 5–10% [1]. A peptic ulcer is a gastrointestinal disease characterized by mucosal damage due to several factors that include pepsin and gastric acid secretions, *Helicobacter pylori* infection, and prolonged use of non-steroidal anti-inflammatory drugs [2]. The pathophysiology of peptic ulcer disease involves an imbalance between offensive (acid, pepsin, and *Helicobacter pylori*) and defensive factors (mucin, prostaglandin, bicarbonate, nitric oxide, and growth factors) [3].

*Nigella sativa* (NS) is a medicinal plant increasingly used in practice, either alone or in combination with many drugs for treating various health problems, such as gastrointestinal, respiratory, metabolic, immune-related, and cardiovascular diseases. [4, 5] *Nigella Sativa* is a member of the Ranunculaceae family with about 14 species in its genus. Among these species, *Nigella sativa* is being extensively investigated for medicinal properties[6]. The plant is native to Southern Europe, Southwest Asia, and North Africa, and it is cultivated and widely used in many Southern European, Middle Eastern, and Asian countries as a spice and food preservative, and in the treatment of disorders and diseases [7]. Various pharmacological studies on *N. sativa* have confirmed its antidiabetic, antitussive, anticancer, antioxidant, hepatoprotective, neuroprotective, gastroprotective, immunomodulator, analgesic, antimicrobial, anti-inflammatory, spasmolytic, and bronchodilator activity [8]. The black seed of NS contains a fixed oil (>30%) and volatile oil (0.40%-0.45%), which contains 18.4% – 24% thymoquinone (TQ), which has antioxidant and anti-inflammatory properties [9], along with gastroprotective activity in rats. [10] The results of a study by Mahmoud Awny Magdy et al. confirmed that, apart from its known antioxidant properties, TQ also has novel gastroprotective mechanisms of proton pump inhibition, reduced acid secretion, and neutrophil infiltration, while enhancing mucin secretion and nitric oxide production, which leads to a reduced ulcer index in treated animals [11]. In another study on Cisplatin (CP)-induced gastrointestinal damage, both NS oil and TQ administration

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to CP-treated rats significantly attenuated CP-induced oxidative stress by suppressing the augmentation in CP-induced LPO, and reversing the inhibitory effect of CP on endogenous antioxidant enzymes [12].

The aim of the current study was to evaluate the ulcer protective effect of NS oil in Albino rats by two methods of ulcer induction. NSAIDs like Aspirin alter the physicochemical properties of the mucous and result in mucosal damage; therefore, Aspirin was utilized in the first method for ulcer induction. It is also known that stress enhances the production of reactive oxygen species that impair the gastric mucosa and induce ulceration; therefore, the forced swim method of acute gastric ulceration was employed as the second method of ulcer induction in the experimental rats.

## MATERIALS AND METHOD

The study was carried out in the postgraduate research laboratory of the Department of Pharmacology, Deccan College of Medical Sciences, after obtaining formal approval from the Institutional Animal Ethics committee (IAEC). Laboratory-bred male Albino Wistar rats were obtained from the central animal house of the Institute. An objective experimental animal study was carried out over a period of 3 months.

**Materials – Preparation of Chemicals.** *Nigella sativa* oil: purchased from Mohammedia Products, Karimnagar. This is a GMP product with a strength of 91 mg/100 ml.

Ranitidine: used as the standard drug [13].

Aspirin: used as a drug to induce ulcers in animal models.

**Experimental animals.** This was an experimental study conducted on 36 laboratory-bred Albino rats (weight: 180 – 220 grams, 6 – 7 weeks old). The animals were maintained under optimal atmospheric and hygienic conditions, with food and water available *ad libitum*. They were acclimatized for a week to the laboratory conditions before the experimental work was carried out.

**Experimental design.** The experimental study was conducted by 2 methods of gastric ulcer induction in rats:

Aspirin-induced gastric ulcers.

Forced swim induced acute gastric ulceration.

**Aspirin-induced gastric ulcers method.** The Albino rats were divided into 3 groups which consisted of 6 rats in each group. All the experimental animals in these groups received their respective pre-treatment for 5 days per oral route at a fixed time of day. Group 1 – control group which received distilled water at 2ml/kg. Group 2 – test group which received *Nigella sativa* oil at 2ml/kg. Group 3 – standard group which received Ranitidine at 20mg/kg. On Day 6, the rats were kept fasting for 24 hours, with free access to water. On day 7, animals in all 3 groups received Aspirin at 200mg/kg [14, 15].

The animals were sacrificed by stunning after 4 hours of Aspirin intake. Their stomachs were excised, cut along the greater curvature, and gently rinsed in tap water. Each stomach was stretched on a piece of cork with the mucosal surface facing up, and examined in a standard position for macroscopic examination. Ulcers scoring was performed with the aid of a magnifying glass.

**Forced swim induced acute gastric ulceration.** The Albino rats were divided into 3 groups, with 6 rats in each group. All the experimental animals in these groups received their respective pre-treatment for 5 days per oral route at a fixed time of day. Group 1 – control group, they received distilled water at 2ml/kg. Group 2 – test group, they received *Nigella sativa* oil at 2ml/kg. Group 3 – standard group, they received ranitidine at 20mg/kg. On Day 6, the experimental rats were kept fasting for 24 hours, with free access to water.

On Day 7, the study animals were forced to swim in a deep jar, filled with water at 23 degrees for 5 hours. These rats were then taken out and sacrificed. Their stomachs were excised, cut along the greater curvature, and gently rinsed in tap water. The stomach was stretched on a piece of cork, with the mucosal surface up, and examined in a standard position for macroscopic examination. Ulcer scoring was performed with the aid of a magnifying glass.

**Measurement of gastric lesions.** According to the method by Kulkarni [16], the ulcer index can be measured using the following scores involving the number and severity of ulcers (Tab. 1).

**Table 1.** Ulcer scoring

| Observation | Score |
|---|---|
| Normal coloured stomach | 0 |
| Red colouration | 0.5 |
| Spot ulcers | 1 |
| Haemorrhagic streak | 1.5 |
| Ulcer with area >3 but ≤5 $mm^2$ | 2 |
| Ulcers with area> 5 $mm^2$ | 3 |

**Calculation of Ulcer index.** Calculated by the following formula UI = UN + US+UP × 10
UI = Ulcer index
UN = Average number of ulcers per animal
US = Average number of severity score
UP = Percentage of animals with ulcers

The percentage protective ratio, given by the following equation:

$$\text{percentage protective ratio} = 100 - \frac{[\text{UI pretreated}] \times 100}{[\text{UI control}]},$$

**Statistical analysis.** The readings show mean ± standard error of means. The Ulcer Mean Index of the treatment groups was determined and compared statistically with that of control by using ONEWAY followed by ANOVA.

## RESULTS

**Aspirin-induced ulcer method.** On gross examination of the stomach of rats in all 3 groups, (control group treated with distilled water,test group treated with *N. sativa* oil, and the standard group treated with Ranitidine) the total mean ulcer score for the control group was 4.25, test (*N. sativa* oil) group – 2.25, and standard drug group – 2. Both the test and standard groups did not develop ulcers bigger than

**Table 2.** Results of Aspirin-induced ulcer method of gastric ulcer induction

| Group No.(n) | Body weight(gm) | Normal coloured stomach | Red colouration | Spot ulcers | Haemorrhagic streak | Ulcer with area >3 but ≤5 mm² | Ulcers with area > 5 mm² | Total score | Mean | Percentage protection |
|---|---|---|---|---|---|---|---|---|---|---|
| CONTROL (6) | 200 | - | 0.5 | 1 | 1.5 | 2 | - | 5 | 4.25± | - |
| | 220 | - | 0.5 | 2 | - | - | - | 2.5 | 0.381 | |
| | 190 | - | 0.5 | 1 | 3 | - | - | 4.5 | | |
| | 210 | - | 0.5 | 1 | 1.5 | 2 | - | 5 | | |
| | 220 | - | 0.5 | 2 | - | 2 | - | 4.5 | | |
| | 195 | - | 0.5 | 2 | 1.5 | - | - | 4 | | |
| TEST (6) | 220 | - | 0.5 | 1 | 1.5 | - | - | 3 | 2.25± | 47.05 |
| | 220 | - | 0.5 | 1 | - | - | - | 1.5 | 0.335 | |
| | 210 | - | 0.5 | 1 | 1.5 | - | - | 3 | | |
| | 195 | - | 0.5 | 1 | - | - | - | 1.5 | | |
| | 180 | - | 0.5 | 1 | - | - | - | 1.5 | | |
| | 180 | - | 0.5 | 1 | 1.5 | - | - | 3 | | |
| STANDARD (6) | 220 | - | 0.5 | 1 | 1.5 | - | - | 3 | 2.00± | 52.9 |
| | 210 | - | 0.5 | 1 | - | - | - | 1.5 | 0.316 | |
| | 220 | - | 0.5 | 1 | 1.5 | - | - | 3 | | |
| | 185 | - | 0.5 | 1 | - | - | - | 1.5 | | |
| | 195 | - | 0.5 | 1 | | - | - | 1.5 | | |
| | 190 | - | 0.5 | 1 | - | - | - | 1.5 | | |

5mm. Percentage protection was calculated to be 47.5% in the *Nigella sativa* group, and 52.9% in the standard group (Tab. 2). Figures 1, 2 and 3 show the gross stomach specimens.

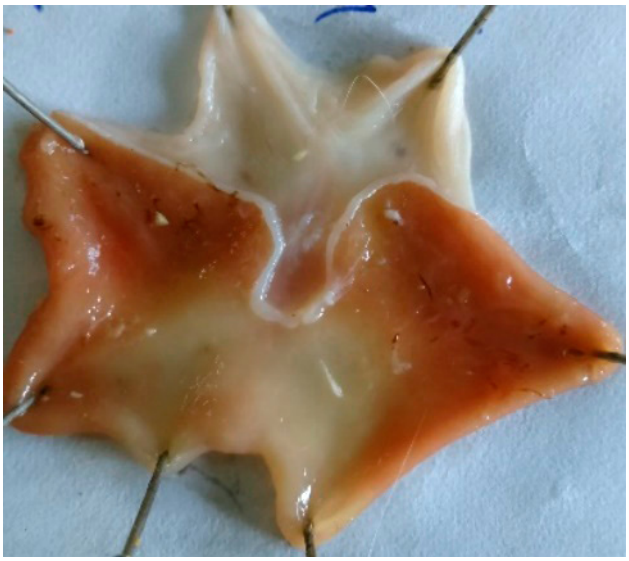

**Figure 1.** Gross stomach specimen of Aspirin-induced gastric ulcer – control group

**Forced swim method.** In the forced swim induced acute gastric ulceration, none of the experimental animals showed normal coloured stomach walls, neither with distilled water, *Nigella sativa* oil, or the standard drug – Ranitidine. Rats in all the groups had ulcers varying between 0.5mm – 5mm. The total mean ulcer score for the *Nigella sativa* group was 6.3, control group – 23.4 and in the Ranitidine group – 7.1. Percentage protection was calculated which in the *Nigella sativa* oil was 73%, and 69.6% in the Ranitidine group (Tabl. 3). Gross stomach specimens are depicted in Figures 4, 5 and 6.

**Analysis of results.** Statistical significance was calculated by applying ANOVA. In the Aspirin-induced gastric ulcers method, the effect of the test drug (*Nigella sativa* oil), in comparison to the control, was statistically significant – 0.03

**Figure 2.** Gross stomach specimen of Aspirin-induced gastric ulcer – standard (Ranitidine) group

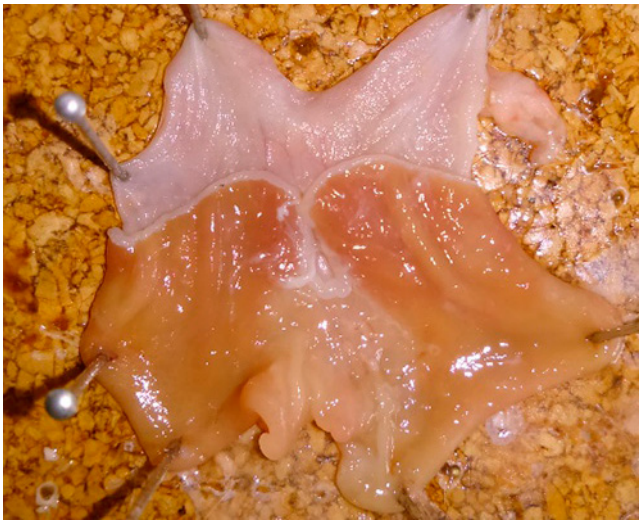

**Figure 3.** Gross stomach specimen of Aspirin-induced gastric ulcer – test (NS oil) group

**Table 3.** Results of the forced swim induced acute gastric ulceration method

| Group No. | Body weight(gm) | Treatment | Normal coloured stomach | Red colouration | Spot ulcers | Haemorrhagic streak | Ulcer with area >3 but ≤5 mm² | Ulcers with area> 5 mm² | Total score | Mean | Percentage protection |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. | 210 | Distilled | - | 0.5 | 10 | 10.5 | 2 | - | 23 | 23.4 | |
| CONTROL | 200 | water | - | 0.5 | 12 | 9 | 4 | - | 25.5 | ± | |
| | 190 | | - | 0.5 | 11 | 7.5 | 4 | - | 23 | .7002 | |
| | 180 | | - | 0.5 | 10 | 9 | 6 | - | 25.5 | | |
| | 190 | | - | 0.5 | 13 | 6 | 2 | - | 21.5 | | |
| | 200 | | - | 0.5 | 12 | 7.5 | 2 | - | 22 | | |
| 2. | 180 | *Nigella* | - | 0.5 | 2 | 3 | - | - | 5.5 | 6.3 | 73 |
| TEST | 200 | *sativa* oil | - | 0.5 | 4 | 1.5 | - | - | 6 | ± | |
| | 190 | | - | 0.5 | 3 | 3 | - | - | 6.5 | .3333 | |
| | 200 | | - | 0.5 | 4 | 3 | - | - | 7.5 | | |
| | 180 | | - | 0.5 | 2 | 4.5 | - | - | 7 | | |
| | 220 | | - | 0.5 | 2 | 3 | - | - | 5.5 | | |
| 3. | 190 | Ranitidine | - | 0.5 | 3 | 3 | - | - | 6.5 | 7.1 | 69.6 |
| STANDARD | 210 | | - | 0.5 | 4 | 1.5 | - | - | 6 | ± | |
| | 220 | | - | 0.5 | 3 | 3 | - | - | 6.5 | .5110 | |
| | 200 | | - | 0.5 | 2 | 4.5 | - | - | 7 | | |
| | 200 | | - | 0.5 | 3 | 6 | - | - | 9.5 | | |
| | 190 | | - | 0.5 | 4 | 3 | - | - | 7.5 | | |

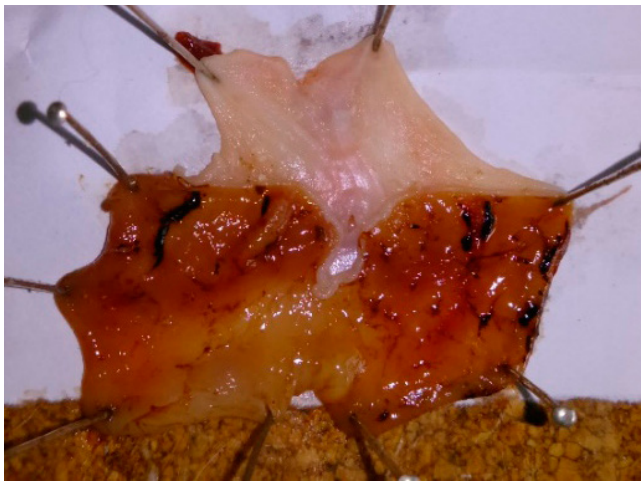

**Figure 4.** Gross stomach specimen of forced swim induced acute gastric ulceration – control group

(P<0.05), but when the test drug was compared with the standard drug, it was not significant – 0.867 (P>0.05). When the effect of the standard drug –Ranitidine, was compared

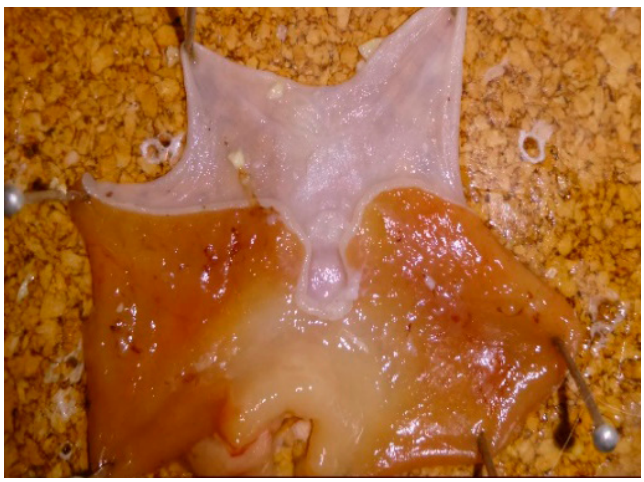

**Figure 5.** Gross stomach specimen of forced swim induced acute gastric ulceration – standard (Ranitidine) group

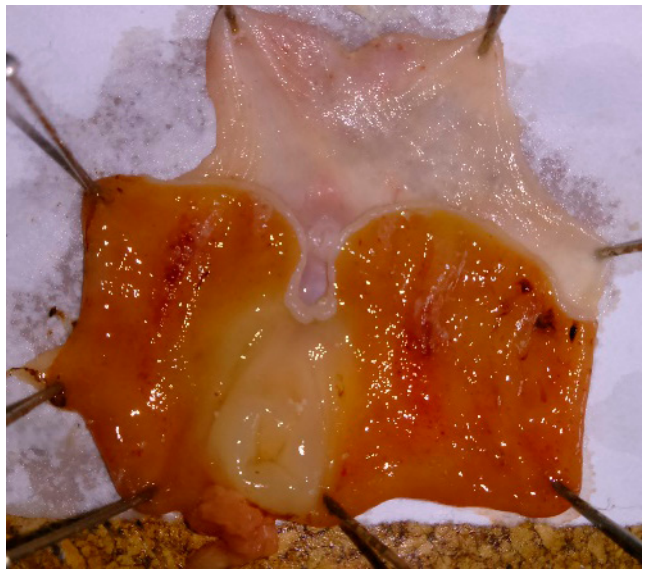

**Figure 6.** Gross stomach specimen of forced swim induced acute gastric ulceration – test (NS oil) group

to the control, it was statistically significant – 0.01(P<0.05). However, when the standard drug was compared to the test drug, it was statistically non-significant – 0.867(P>0.05) (Tab. 4, Fig. 1).

In the forced swim induced acute gastric ulceration, the effect of *Nigella sativa* oil in comparison to the effect of control it was statistically significant (P<0.05; 0.03), whereas in comparison to the effect of the standard drug, Ranitidine, it was statistically not significant (P>0.05; 0.529) (Tab. 5, Fig. 2).

When the anti-ulcer effects of the standard drug (Ranitidine) were compared with the anti-ulcer effect of the control (distilled water), it was statistically significant, but when the ant-iulcer effects of the standard drug (Ranitidine) were compared to the test (NS oil), it was statistically insignificant (P>0.05; 0.529).

Therefore, *Nigella sativa* has anti-ulcer activity. However, there is no statistical significance between the standard drug Ranitidine and *Nigella sativa* oil, which suggests that there

**Table 4.** Aspirin-induced gastric ulcers method – Multiple Comparisons

| (I) Groups | (J) Groups | Mean Difference (I–J) | Std. Error | Significance | 95% Confidence Interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Upper Bound |
| CONTROL | TEST | 2.00000* | .48876 | 0.003 | .7305 | 3.2695 |
| | STANDARD | 2.25000* | .48876 | 0.001 | .9805 | 3.5195 |
| TEST | CONTROL | -2.00000* | .48876 | 0.003 | -3.2695 | -.7305 |
| | STANDARD | .25000 | .48876 | 0.867 | -1.0195 | 1.5195 |
| STANDARD | CONTROL | -2.25000* | .48876 | 0.001 | -3.5195 | -.9805 |
| | TEST | -.25000 | .48876 | 0.867 | -1.5195 | 1.0195 |

**Table 5.** Forced swim induced acute gastric ulceration of ulcer induction – Multiple comparisons

| (I) Groups | (J) Groups | Mean Difference (I-J) | Std. Error | Significance | 95% Confidence Interval | |
|---|---|---|---|---|---|---|
| | | | | | Lower Bound | Upper Bound |
| CONTROL | TEST | 17.0833* | .7583 | 0.000 | 15.114 | 19.053 |
| | STANDARD | 16.2500* | .7583 | .000 | 14.280 | 18.220 |
| TEST | CONTROL | -17.0833* | .7583 | 0.000 | -19.053 | -15.114 |
| | STANDARD | -.8333 | .7583 | 0.529 | -2.803 | 1.136 |
| STANDARD | CONTROL | -16.2500* | .7583 | 0.000 | -18.220 | -14.280 |
| | TEST | .8333 | .7583 | 0.529 | -1.136 | 2.803 |

* Mean difference significant at 0.05 level

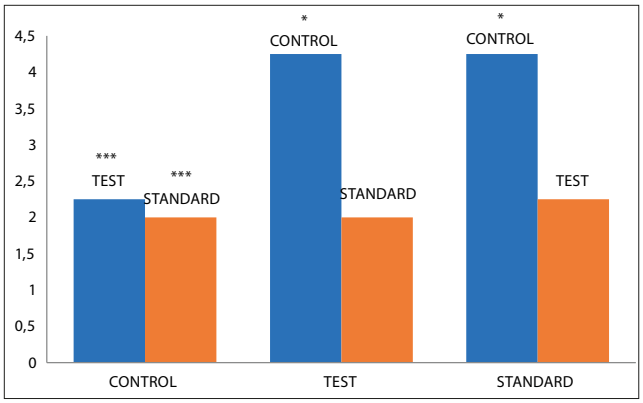


**Figure 1.** Results of Aspirin-induced ulcer method of gastric ulcer induction Treatment groups. Ulceration score – n ± SD; Treatment group = 6; *** highly significant; *significant

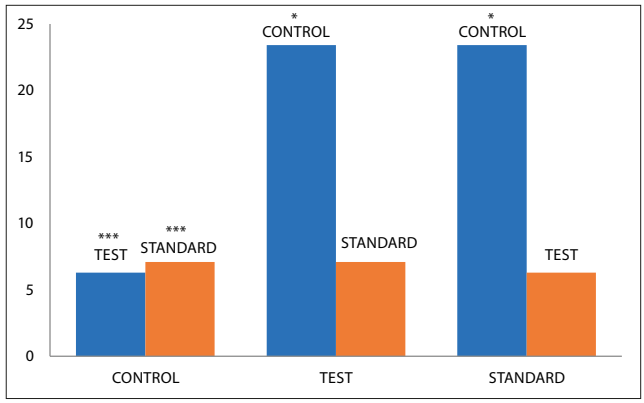


**Figure 2.** Results of the Forced swim induced acute gastritis ulceration method. Treatment groups *** Highly significant; *significant

is similar protection offered by both drugs in the models of anti-ulcer evaluation techniques.

## DISCUSSION

*Nigella sativa* oil has a plethora of health benefits and has been utilized in the treatment of several diseases, including asthma, fever, bronchitis, diabetes, chest congestion, dizziness, paralysis, chronic headache, back pain, and inflammation. The current study evaluated the anti-ulcer potential of NS oil in Albino rats by using 2 methods. In the first method of Aspirin-induced ulcers, Aspirin administration causes mucosal damage by interfering with prostaglandin synthesis, increasing acid secretion and back diffusion of H+ ions, and thus leading to the breaking- up of the mucosal barriers [17]. Inhibitions of prostaglandin synthesis by Aspirin coincide with the earlier stages of damage to the cell membrane of mucosal, parietal, and endothelial cells. Prostaglandin is a major component of the protective factors that maintain gastrointestinal mucosal integrity and microcirculation [18]. A study by Ibrahim A Al Mofleh et al. indicated that there is a probable local increase in prostaglandin synthesis by the NS [19]. This was observed during the Aspirin-induced gastric ulcers method – that there was a remarkable and significant change in the mean value of ulcer numbers in rats treated with *Nigella sativa* oil and Ranitidine, compared to rats provided with distilled water. The percentage protection ratio by NS oil was 47.05 % and that of the standard drug – 52.9 %. The results of this study are similar to the study by Orooba MS Al-Shaha et al. [20], Nahid Sultana et al. [21], and Mehmat Kanter et al. [22].

In the second method, forced swim induced acute gastric ulceration, stress involved both psychological and physiological responses leading to gastric ulceration. The psychological responses include anxiety, depression, feeling of helplessness, fear, and the threat of drowning. The physiological responses are neuro-hormonal and

immunological activations, and the involvement of Corticotropin-releasing factors. [23] These two systems may interact during stressful challenges [24, 25], known as psychosomatic reactions, which lead to gastric ulcerations.

Studies also suggest disturbances in gastric mucosal microcirculation, alteration of gastric secretion, and abnormal gastric motility to be the pathogenic mechanisms responsible for stress-induced gastric mucosal lesions, and gastric mucus depletion [26]. In the current study, during the forced-swim test of gastric ulcer induction, it was found that the percentage protection offered by NS oil was 73%, and the percentage protection by the standard drug was 69.3%. These results are similar to the gastroprotective effects of methanolic extract of leaves of Catharanthus Roseus in experimental rats conducted by Mahathi et al. [27]. The gastro-protective effect observed in the present study might be due to a possible relationship between mucosal injury, inhibition of acid secretion, and the antioxidant nature of NS [28]. Although this study establishes that NS oil has gastro-protective effects, it has certain limitations in that biochemical analysis of the stomach contents for gastric acidity could not be performed.

## CONCLUSION

Based on the present study, both methods demonstrated that the protection percentage offered by the NS oil is significant and comparable to that of the standard drug used in the treatment of gastric ulcers. Therefore, the active constituent of *Nigella sativa* oil should be explored further to develop gastro-protective medications at commercial levels.

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