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STUDY OF THE NIGELLA SATIVAL OIL ON GASTRIC SECRETION AND GASTRIC MUCOSAL LESION INDUCED BY ORAL INDOMETHACIN IN ALBINO RATS

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INTRODUCTION

The black seed (Nigella sativa), a member of the Runuculaceae family, is an annual plant growing in countries bordering the Mediterranean sea (**Jansen, 1981**). It is one of the native plants that are widely distributed in Egypt (**Hashem and El-Kiey, 1982**). In Arabian folk medicine, the black seed and its constituents, especially oils, have been used for treatment of many diseases such as diabetes, hypertension, bronchial asthma and rheumatism (**Hashem and El-Kiey, 1982**). Moreover, Nigella sativa seeds are digestive stimulants as well as carminative, diuretic, anti-helmintic, antitumor activity (**Hassan and El-Dakhakhny, 1992**), an immune modulating effect (**El-Kadi et al., 1987**) and cytoprotective effect on tissues exposed to cytotoxic agents (**El-Kadi et al., 1987**). It is reported that the seeds contain fixed and volatile oils which contain thymoquinone (**El-Dakhakhny, 1995**). It has been reported that thymoquinone protects organs sgainst oxidative damage induced by a variety of free radical generating agents (**El-Tahir et al., 1993**). It was reported also that thymoquinone has an anti-inflammatory activity in rats and inhibits eicosanoids generation in leukocytes (**Ligumsky et al., 1995**) and non enzymatic peroxidation in brain phospholipid liposomes (**Kolbasa et al., 1998**). Thymoquinone reduces free radical generation especially hydroxyl radicals. These hydroxyl radicals are known to play a major role in the pathogenesis of gastric mucosal ulcer (**Kolbasa et al., 1998**).

Indomethacin is widely used in treating many diseases as rheumatic diseases, gout and fevers. Many toxic and side effects can be seen due to the use or abuse of indomethacin, especially those related to the gastrointestinal tract due to its local

irritant effect, that leads to gastric erosion and ulceration (**Houghton et al., 1995**). It is clear that Nigella sativa has a very low toxicity on oral administration (**Zaoui et al., 2002**), so the present work was done to study the ability of Nigella sativa oil as a cytoprotective agent against oxidative gastric mucosal damage induced by local irritant effect of indomethacin in albino rats. Also, the study of the histological effect of indomethacin on gastric mucosa and effect of Nigella sativa oil on gastric mucosal lesion induced by indomethacin were studied.

MATERIAL AND METHODS

The present study was carried out on 28 adult male albino rats weighing 200 - 250 gm, kept for two weeks under optimal environmental conditions for accommodation. Rats were fed on a diet consisting of wheat and bread soaked in milk. The animals had free access to water. The rats were divided into four equal groups :

Group 1 :

The animals received oral 1 ml saline daily for two weeks and served as control group.

Group 2 :

The animals received oral Nigella sativa oil obtained from Pharco pharmaceutical - Alexanria - Egypt in a dose of 0.88 gm / kg. B.W. aily (**El-Dakhakhny et al., 2000**) for two weeks.

Group 3 :

The animals received oral indomethacin capsules (Memphis - Cairo) in a dose of 30 mg / kg. B.W. daily (**Ahmed and Mahmoud, 1998**) for two weeks.

Group 4 :

The animals received oral Nigella sativa oil in a dose of 0.88 gm / kg. B.W. and oral indomethacin capsules in a dose of 30 mg / kg. B.W. daily for two weeks. The rats remained without food for one day prior to ether anesthesia (except for water) to avoid mixing of food with the gastric secretions, then the gastric secretion was collected according to the method of **Niida et al., (1991)**.

Briefly, abdomen was incised and both the stomach and duodenum were exposed. An acute fistula (inside diameter = 3 mm) made with a polyethene tube,

inserted into the stomach from a small incision made in the duodenum and held in place by a ligature around the pylorus. The esophagus was clamped to prevent reflux and loss of gastric secretion. The gastric secretion was collected every hour for four hours to get an enough amount for the analysis. The following parameters were determined :

1. Volume of gastric secretion, and gastric free acidity according to the method of **Varley (1969)**.
2. Gastric peptic activity according to the method of **Sanyal et al. (1971)**.
3. Mucin content of gastric secretion according to the method of **Richard (1959)**.
4. Gastric mucosal histamine by florometric method of **Lorenz et al. (1971)**.
5. Gastric glutathione content according to the method of **Owens and Belcher (1965)**.

Histological procedures :

The gastric tissue samples were preserved in 10% formol saline and processed for paraffin block preparation. The sections were stained by haematoxylin & eosin (H & E), then examined for histological changes.

Statistical Analysis :

Student's "t" test was used for the evaluation of statistical significance. Differences were considered significant at $P < 0.05$ level. All values were expressed as means ± SE.

RESULTS

1. Effects of oral administration of Nigella sativa oil on volume of gastric secretion (ml / h) in albino rats treated by oral indomethacin :

Administration of oral Nigella sativa oil daily for two weeks in a dose of 0.88 gm / kg. B. W. in albino rats produced non-significant effect on the volume of gastric secretion, ($P > 0.05$). Oral administration of indomethacin produced a significant increase in the volume of the gastric secretion which decreased significantly after combination of oral Nigella sativa oil and indomethacin ($P < 0.05$), (Table 1) & (Fig. 1).

2. Effects of oral administration of Nigella sativa oil on gastric free acidity (μ M / L) *in albino* rats treated by oral indomethacin :

Oral administration of Nigella sativa oil daily for two weeks produced a non-significant change in the gastric free acidity ($P > 0.05$). Oral administration of indomethacin produced a significant reduction in the gastric free acidity after two weeks, compared to control ($P < 0.05$). After giving of oral Nigella sativa oil and indomethacin, there is significant increase in gastric free acidity ($P < 0.05$) (Table 2) & (Fig. 2).

3. Effects of oral administration of Nigella sativa oil on gastric peptic activity (ml / h) in albino rats treated by oral indomethacin :

Oral administration of Nigella sativa oil daily for two weeks produced a non-significant change in peptic activity. Indomethacin administration produced a significant increase in the gastric peptic activity compared to control ($P < 0.05$). A significant reduction of gastric peptic activity was observed after oral administration of Nigella Sativa oil and indomethacin compared to oral indomethacin ($P < 0.05$) (Table 3) & (Fig. 3).

4. Effects of oral administration of Nigella sativa oil on gastric glutathione (mg / gm tissue) in albino rats treated by oral indomethacin :

Oral administration of Nigella sativa oil daily for two weeks produced a significant increase of the gastric glutathione content compared to the control ($P < 0.05$). Oral indomethacin administration for two weeks produced a significant reduction in the gastric glutathione content ($P < 0.05$). Oral administration of Nigella sativa oil with indomethacin produced a significant increase of the gastric glutathione content compared to oral indomethacin ($P < 0.05$). (Table 4) & (Fig. 4).

5. Effects of oral administration of Nigella sativa oil on the gastric histamine content (mg / gm tissue) in albino rats treated by oral indomethacin :

Oral administration of Nigella sativa oil daily for two weeks produced a significant decrease in the gastric histamine content compared to control ($P < 0.05$). Oral administration of indomethacin ddaily for two weeks produced a significant increase in the gastric histamine content compared to control ($P < 0.05$). A significant reduction was observed after oral administration of indomethacin and Nigella sativa oil compared to oral indomethacin ($P < 0.05$) (Table 5) & (Fig. 5).

6. Effects of oral administration of Nigella sativa oil on gastric mucin content (mg hexose %) in albino rats treated by oral indomethacin :

Oral administration of Nigella sativa oil daily for two weeks produced significant increase of the gastric mucin content compared to control ($P < 0.05$). Oral administration of indomethacin produced a significant reduction of the gastric mucin content compared to control ($P < 0.05$). There was significant increase of the gastric mucin content after administration of Nigella sativa oil and indomethacin compared to oral indomethacin, ($P < 0.05$), (Table 6) & (Fig. 6).

Histological Examination :

1. Control Stomach :

The surface epithelial cells which are mucus secreting cells formed a continuous epithelial sheet that covered the gastric surface and line pits of gastric glands. All the cells of the surface, gastric pits and gastric glands were intact and normal. There was no evidence of erosions or hemorrhages in the gastric mucosa (Figs. 7 - a & b).

2. Effects of oral administration of Nigella sativa oil on gastric mucosa :

As control group.

3. Effects of oral administration of indomethacin on gastric mucosa :

Histological examination revealed mucosal damage in the form of superficial erosions (Fig. 8 - a). These erosions (ulcers) were multiple, small in size and not reaching the muscularis mucosa layer. Subepithelial tissues showed hemorrhage, edema and the blood vessels are numerous and dilated. There is mononuclear cellular infiltration in the lamina propria of the gastric mucosa. Gastric glands are reduced in number. The glands present all are abnormal in morphology and distribution. Some areas showed hyperplastic gastric glands, (Fig. 8 - b). Other areas showed gastric ulceration covering a bier like network of hyperplastic and metaplastic gastric pits (Fig. 8 - c). Third areas revealed marked destruction of the upper parts of the gastric glands, (Fig. 8 - d).

5. Effects of oral administration of Nigella sativa oil with indomethacin on gastric mucosa :

There was renewal of epithelium to line the surface of the stomach and gastric pits again. Also there was a significant increase in the gastric glands and return of

these gastric glands to the control pattern. No evidences of erosions (ulcerations) (Fig. 9).

Table 1 : Effects of oral administration of Nigella sativa oil on volume of gastric secretion (ml / h) in albino rats treated by indomethacin.

	Mean	S.D ±	S.E. ±	T_1	T_2
Control	**1.44**	0.13	0.05		
NSO	**1.38**	0.13	0.05	0.85	
Indomethacin	**2.6**	0.21	0.08	12.8*	
NSO + Indomethacin	**1.85**	0.12	0.04	6.8*	0.3*

NSO = Nigella sativa oil.

* = Significant ($P < 0.05$).

T1 = NSO, or indomethacin, or NSO + indomethacin compared to control.

T2 = NSO + indomethacin compared to indomethacin.

Table 2 : Effects of oral administration of Nigella sativa oil on gastric free acidity (mEq / L) in albino rats treated by indomethacin.

	Mean (6)	S.D ±	S.E. ±	T_1	T_2
Control	**34.1**	1.03	0.39		
NSO	**33.5**	1.2	0.45	1.01	
Indomethacin	**28.8**	01.91	0.34	10.3*	
NSO + Indomethacin	**35.4**	0.77	0.29	2.7*	15*

* = Significant ($P < 0.05$).

Table 3 : Effects of oral administration of Nigella sativa oil on peptic activity (μM / L) in albino rats treated by indomethacin.

	Mean (6)	S.D ±	S.E. ±	T_1	T_2
Control	**79.2**	1.79	0.68		
NSO	**78.7**	1.1	0.42	0.63	
Indomethacin	**85.5**	1.71	0.65	6.7*	
NSO + Indomethacin	**80.1**	0.95	0.73	0.9	5.5*

* = Significant ($P < 0.05$).

Table 4 : Effects of oral administration of Nigella sativa oil on glutathione content in (mg / gm tissue) in albino rats treated by indomethacin.

	Mean (6)	S.D ±	S.E. ±	T_1	T_2
Control	**0.66**	0.02	0.009		
NSO	**0.91**	0.03	0.01	25*	
Indomethacin	**0.38**	0.02	0.01	8*	
NSO + Indomethacin	**0.69**	0.02	0.008	3*	31*

* = Significant ($P < 0.05$).

Table 5 : Effects of oral administration of Nigella sativa oil on gastric histamine content (mg / gm tissue) in albino rats treated by indomethacin.

	Mean (6)	S.D ±	S.E. ±	T_1	T_2
Control	**31.0**	2.16	0.81		
NSO	**24.0**	1.41	0.53	7.2*	
Indomethacin	**34.5**	1.39	0.52	3.6	
NSO + Indomethacin	**27.2**	1.79	0.68	3.6*	8.5*

* = Significant ($P < 0.05$).

Table 6 : Effects of oral administration of Nigella sativa oil on gastric mucin content (mg / hexose %) in albino rats treated by indomethacin.

	Mean (6)	S.D ±	S.E. ±	T_1	T_2
Control	**51.0**	2.16	0.37		
NSO	**72.5**	2.22	0.84	23.6*	
Indomethacin	**38.7**	1.97	0.74	15.0*	
NSO + Indomethacin	**59.2**	1.79	0.68	10.6*	20.5*

* = Significant ($P < 0.05$).

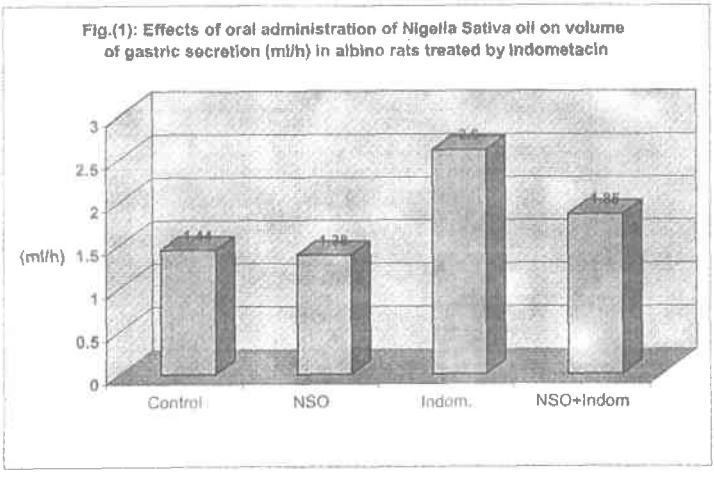

Fig. (1) : Effects of oral administration of Nigella Sativa oil on volume of gastric secretion (ml / h) in albino rats treated by indometacin.

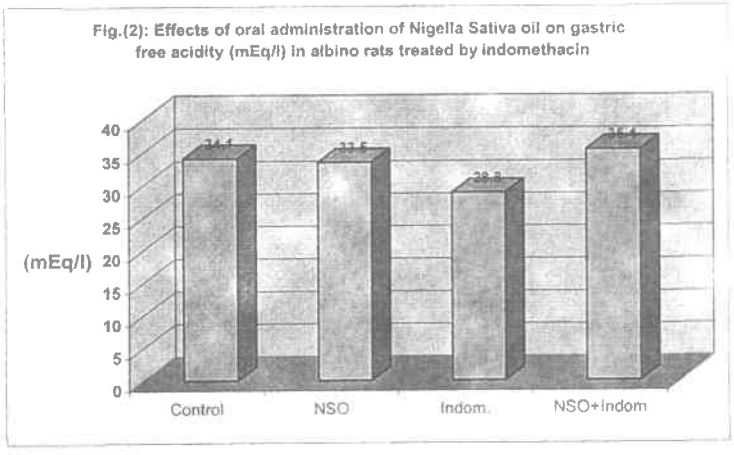

Fig. (2) : Effects of oral administration of Nigella Sativa oil on gastric free acidity (mEq / l) in albino rats treated by indometacin.

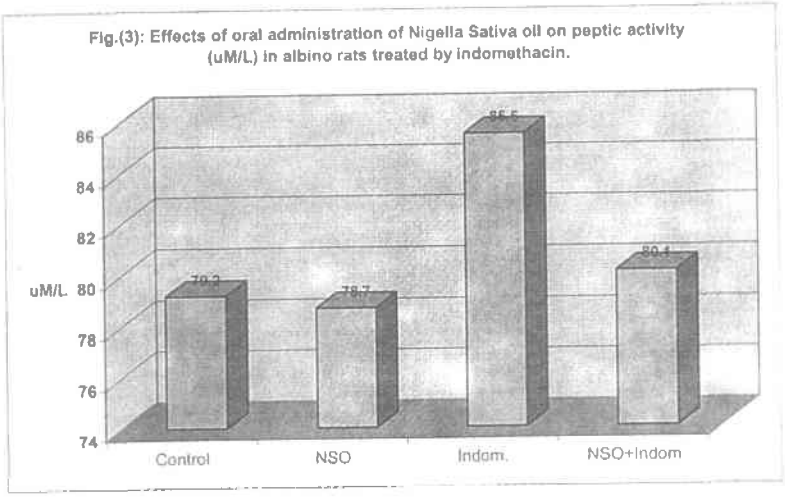

Fig. (3) : Effects of oral administration of Nigella Sativa oil on peptic activity (µM / L) in albino rats treated by indometacin.

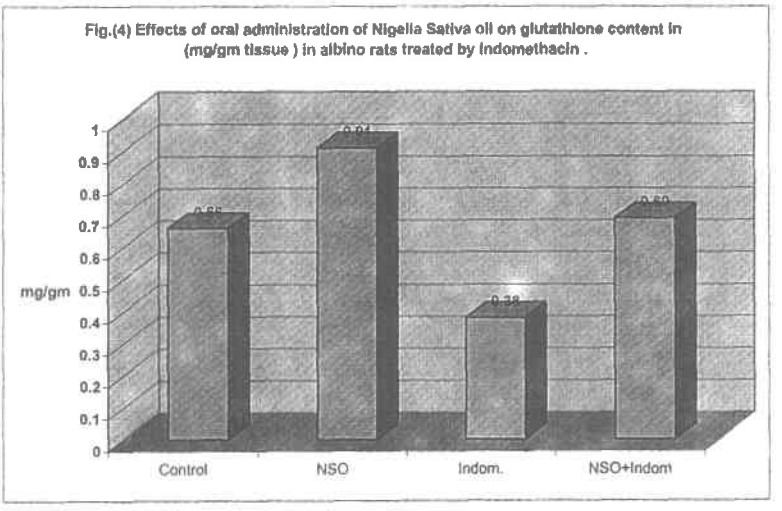

Fig. (4) : Effects of oral administration of Nigella Sativa oil on glutathione content in (mg / gm tissue) in albino rats treated by indometacin.

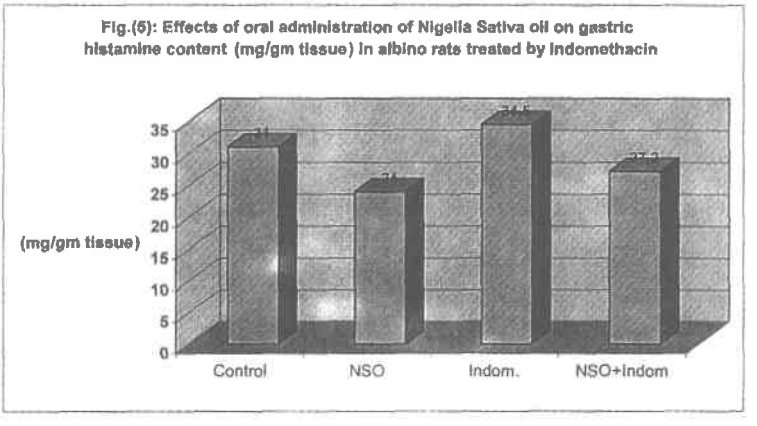

Fig. (5) : Effects of oral administration of Nigella Sativa oil on gastric histamine content (mg / gm tissue) in albino rats treated by indometacin.

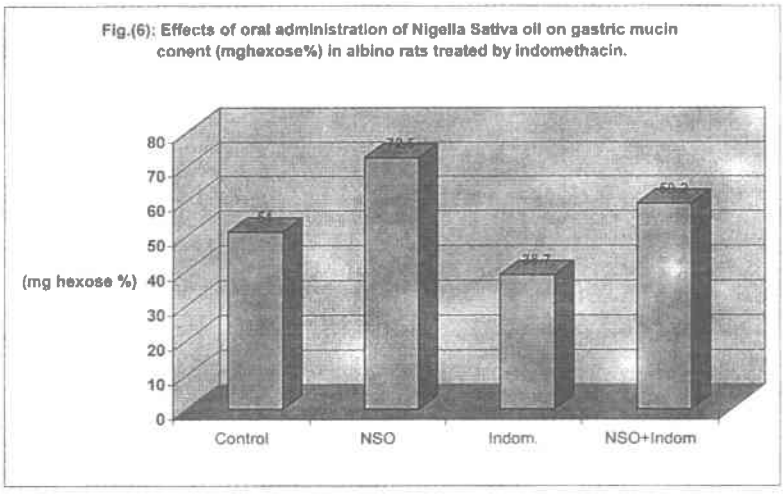

Fig. (6) : Effects of oral administration of Nigella Sativa oil on gastric mucin content (mg / hexose %) in albino rats treated by indometacin.

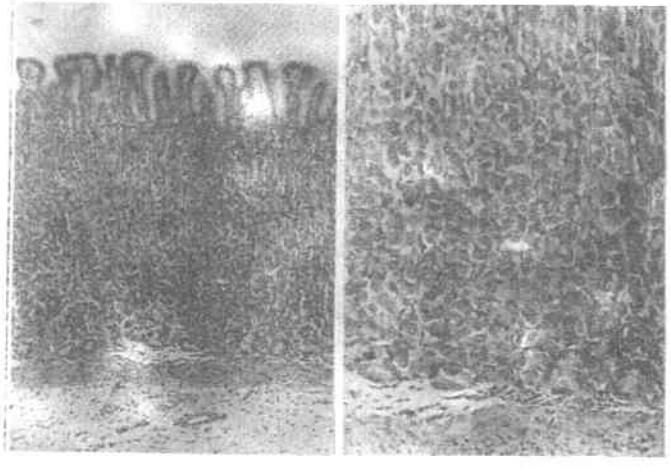

Fig. (7 - a) : A photograph of gastric mucosa from a control rat. The mucosa shows, that the surface mucus secreting cells form a continuous epithelial sheet that cover the gastric surface and line the pits. All the cells on the surface, in gastric pits and gastric glands are intact and normal. There is no evidence of erosion or hemorrhage in the mucosa.

(H. & E., x 100)

Fig. (7 - b) : Higher magnification showing the morphology of control gastric glands.

(H. & E., x 200)

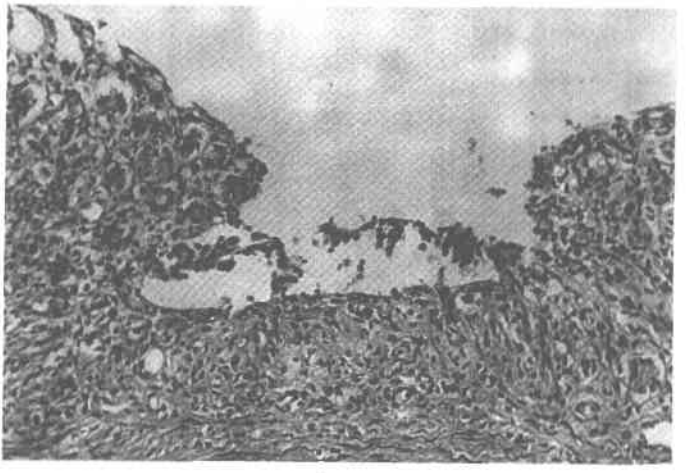

Fig. (8 - a) : A photomicrograph of a section of gastric mucosa from a rat received indomethacin, showing ulcerated mucosal covering. The lamina propria shows mononuclear cellular infiltration.

(H. & E., x 200)

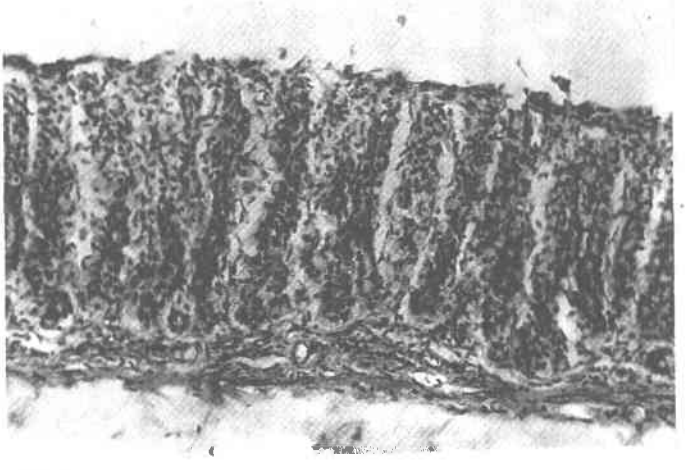

Fig. (8 - b) : A photomicrograph of haematoxylin and eosin stained section of gastric mucosa from a rat received Indomethacin, Showing hyperplastic gastric glands.

(x 200)

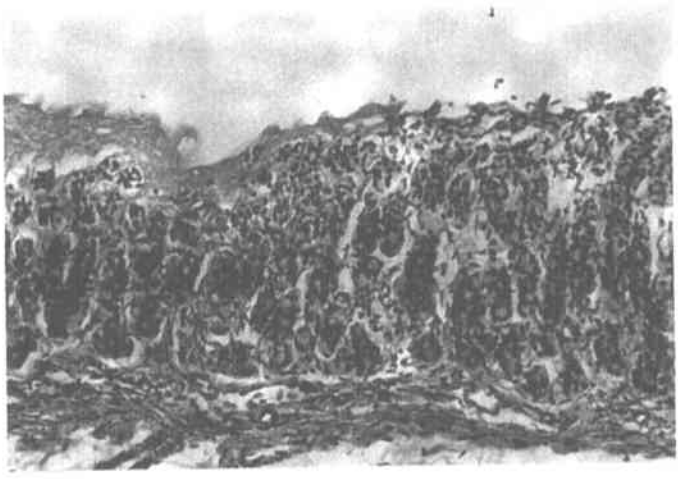

Fig. (8 - c) : A photomicrograph of gastric mucosa from a rat treated with indomethacin, revealed gastric ulceration covering a bier like network of hyperplastic and metaplastic gastric glands.
(H. & E., x 200)

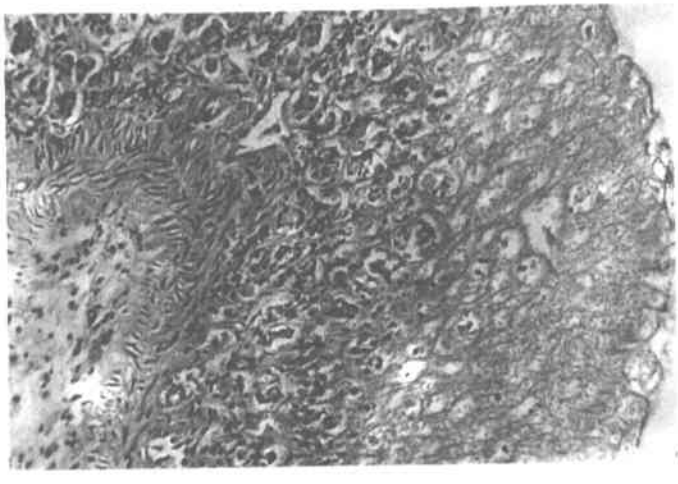

Fig. (8 - d) : A photomicrograph of heamatoxylin and eosin stained section of gastric mucosa from a rat administrated indomethacin reveals destruction of the upper parts of the gastric glands. Note the muscularis mucosa.
(x 400)

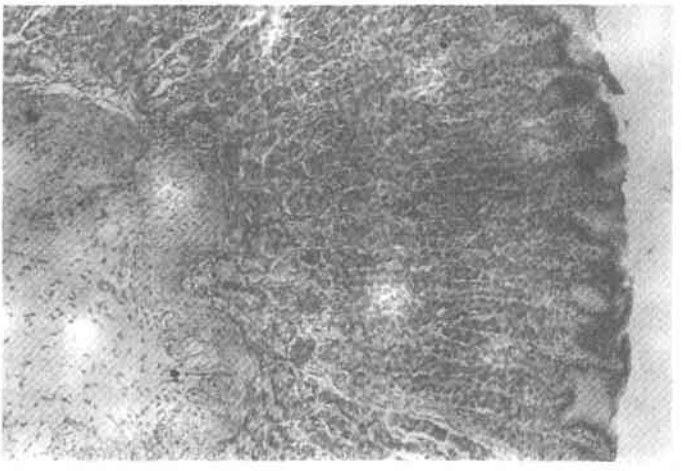

Fig. (9) : A photomicrograph of gastric mucosa from a rat administrated indomethacin with Nigella Sativa oil showing more or less normal gastric glands. There is no evidence of hemorrhage or ulceration.

(H. & E., x 200)

DISCUSSION

Indomethacin has been widely used to induce experimental gastric lesion in animals (**Cho et al., 1985**). A deficiency of endogenous prostaglandin (PGs) is widely accepted as a major factor in the pathogenesis of gastrointestinal lesions caused by indomethacin. A small amount of exogenous PGs prevents the induction and further development of gastric ulceration (**Vankolfschoten et al., 1983**).

The present study revealed that oral administration of Nigella sativa oil for 2 weeks increased gastric mucin content and glutathione level, while the gastric mucosal histamine content and volume were reduced. At the same time there were non-significant change in free acidity and peptic activity of the gastric guice. These results can explain the protective effect of Nigella sativa oil against the indomethacin induced gastric damage in a manner similar to that observed with PGs (**Vankolfschoten et al., 1983**), by counteracting indomethacin induced inhibition of PGs synthesis. The increased glutathione level is in agreement with **EL-Tahir et al. (1993)** who proved the antioxidative, and cytoprotective (**El-Kadi et al., 1987**) effect of Nigella sativa oil through increased glutathione level.

The decrease in the gastric mucosal histamine is in agreement with that of **Charkaraverty (1993)** who proved that Nigella sativa and one of its constituents

(polythymoquinone) in relatively low concentration inhibited in vitro histamine release from rat peritoneal mast cells. Moreover, Nigella sativa oil induced inhibition of histamine release due to inhibition of adenylate cyclase on stimulation of phosphodiesterase activity (**Satoch et al., 1981**).

Indomethacin administration produced changes in the physiology of gastric mucosa in the form of reduction in free acidity, mucin content and glutathione level, as well as it produced an increase in gastric histamine content and peptic activity of the stomach.

Administration of Nigella sativa oil with indomethacin resulted in increased gastric mucin content and glutathione level, while the histamine content was decreased. This explained the protective effect of Nigella sativa oil against indomethacin induced ulcer. The role of Nigella sativa might be explained by the increased glutathione level in gastric mucosa. This increase in glutathione level occurred by reduction of glutathione depletion. This caused a decrease in indomethacin induced gastric damage as reported by **Jimmy et al. (1997)**. Glutathione has a role in synthesis of PGs (**Cho et al., 1985**) through prostaglandin synthetase which is capable of synthesizing PGE2 (**Ghamdi, 2001**).

The increase of PGE2 by Nigella sativa oil was proved by **El-Dakhakhny et al. (2000) and El Sayed (1998)** who reported that treatment of normal and sensitized animals by Nigella sativa oil showed marked increase in PGE2 in the perfused guinea pig lung, so it is clear that peostaglandins have an essential role in the protection of gastric mucosa against indomethacin (**Alarcon et al., 1993**). Moreover, the decrease of gastric mucosal histamine level by Nigella sativa oil has a gastric protective action, which reduces gastric ulcer (**Charkaraverty, 1993**), in addition to the protective effect of gastric mucin that is increased by Nigella sativa oil (**El-Dakhakhny et al., 2000**).

This study showed that administration of indomethacin alone (group 3) caused histological changes in the form of multiple superficial small ulcers, destruction of the upper parts of the gastric glands but there was hyperplasia of the lower parts of the glands. There was edema, hemorrhage and mononuclear cellular infiltration in the lamina propria of the gastric mucosa. All these gastric changes most probably due to decreased glutathione level (**Jimmy et al., 1997**), increased peptic activity, local irritant effect and decreased gastric mucin content (**El-Dakhakhny et al., 2000**) induced by indomethacin.

The mechanism by which indomethacin induces gastric injury is generally considered to involve also depletion of PGs, yet it has been proven more complicated

than expected and involves multiple, closely interacting elements such as gastric hypermotility, microcirculatory disturbances, neutrophil-endothelial cell interactions, and superoxide radicals, in addition to PG deficiency (**Ludmila et al., 2002**).

The present study revealed that the morphological appearance is markedly improved by administration of Nigella sativa oil with indomethacin as the gastric glands returned more or less to the control pattern. The improvement was due to elevation of glutathione level again, devreased peptic activity and increased gastric mucin content.

It is concluded that treatment with indomethacin produced both physiological and morphological damage to the gastric mucosa. Moreover, Nigella sativa oil caused marked improvement of these changes. It is advisable to use Nigella sativa oil as an adjuvant therapy with indomethacin to prevent occurrence of gastric ulceration especially if it is used for long duration.

SUMMARY

The present work was done to study the possible effects of Nigella sativa oil on gastric secretion and gastric mucosal lesion caused by pral indomethacin in albino rats. The study was conducted on 28 adult male albino rats. The animals were divided into four aqual groups :

Group (1) received 1 ml saline orally for two weeks (control), group (2) received Nigella sativa oil in a dose of 0.88 gm / kg. B.W. orally daily for 2 weeks, group (3) received indomethacin in a dose of 30 mg / kg. B.W. orally daily for two weeks, group (4) received Nigella sativa oil followed by indomethacin in the same doses orally daily for two weeks. Under light ether anesthesia, the abdomen was incised and both the stomach and duodenum were exposed. An acute fistula (inside diameter = 3 mm) made with a polyethene tube, inserted into the stomach from a small incision made in the duodenum and held in place by a ligature around the pylorus. The esophagus was clamped to collect the gastric juice. After four hours, the secretion of the stomach was collected for determination of volume, free acidity, mucin content and peptic activity. Then the rats were decapitated, and gastric mucosa was scrubbed for estimation of mucosal histamine and glutathione levels. Gastric tissues were prepared and examined for histological changes.

The results showed that the oral administration of Nigella sativa oil in albino rats produced a significant increase in mucin content and glutathione level and a significant decrease in volume of gastric secretion and mucosal histamine content.

Indomethacin administration produced a significant reduction in free acidity and glutatione level while it produced a significant increase in mucosal histamine content. Histological examination showed damage to gastric surface epithelium, destruction of gastric glands and subepithelial congestion, hemorrhage and edema. After animals were protected with Nigella sativa oil with indomethacin (group 4), there was a significant increase in glutathione level, mucin content an free acidity and a significant decrease in gastric mucosal histamine content. Also, there was marked improvement of histological picture with no evidence of hemorrhage, or erosion and return of gastric glands to the control pattern. It is recommended to use <nigella sativa oil as an adjuvant therapy with indomethacin to prevent development of gastric ulceration.

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دراسة عن تاثير زيت حبة البركة على إفرازات المعدة وعلى تغيرات الغشاء المخاطى الناتجة عن تناول عقار الايندوميثاسين فى الفئران البيضاء

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يهدف هذا البحث لدراسة تأثير تناول زيت حبة البركة بالفم على إفرازات المعدة وعلى الغشاء المخاطى المبطن لجدار المعدة فى الفئران البيضاء التى أعطيت عقار الايندوميثاسين عن طريق الفم . وقد أجرى البحث على ٢٨ من ذكور الفئران البيضاء وقد قسمت الفئران إلى أربعة مجموعات متساوية :

المجموعة الأولى : أعطيت محلول الملح ١ سم عن طريق الفم يوميا لمدة أسبوعين واعتبرت مجموعة ضابطة .

المجموعة الثانية : وقد تم إعطاؤها زيت حبة البركة يوميا عن طريق الفم بجرعة تساوى ٨٨ر جم / كجم من وزن الجسم لمدة أسبوعين .

المجموعة الثالثة : وقد تم إعطاؤها الاندوميثاثين يوميا عن طريق الفم بجرعة تساوى ٣٠ مجم / كجم من وزن الجسم لمدة أسبوعين .

المجموعة الرابعة : وقد تم إعطاؤها زيت حبة البركة والاينوميثاسين بنفس الجرعات السابقة عن طريق الفم لمدة أسبوعين .

وفى نهاية البحث تم تخدير الفئران بالاثير وتم ربط فتحة البواب وجمع الإفرازات المعدية كل ساعة وبعد ٤ ساعات ذبحت الفئران وتم تجميع إفرازات المعدة وذلك لتعيين حجمها ودرجة الحموضة والمخاط ونشاط الأنزيم (pepsin) كما كشطت الأغشية المخاطية لتعيين نسب كل من الجلوتاثيون والهيستامين وأخذت عينات من المعدة وتم تحضيرها وذلك للفحص المجهرى .

وقد دلت نتائج البحث على أن تناول زيت حبة البركة فى الفئران أدى إلى زيادة ملحوظة (له دلالة إحصائية) فى نسبة كل من المخاط والجلوتاثيون وانخفاض ملحوظ (نو دلالة إحصائية) فى حجم ونسبة الهيستامين . وبعد تناول عقار الايندوميثاسين فقد نتج هبوط ملحوظ فى كل من الحموضة والجلوتاثيون وزيادة ملحوظة فى نسبة الهيستامين .

أما بالفحص المجهرى فقد شوهد نزيف وقرح فى الغشاء المخاطى المبطن للمعدة .

وبالنسبة للفئران التى اعطيت كل من زيت حبة البركة والايندوميثاسين فقد دلت النتائج على وجود زيادة ملحوظة فى نسبة كل من الجلوتاثيون والمخاط والحموضة وكان هناك هبوط ملحوظ فى نسبة الهيستامين وتحسن فى الفحص المجهرى وعدم وجود دلائل على القرح أو النزيف . ولذلك يوصى المرضى الذين يتناولون عقار الايندوميثاسين بتناول زيت حبة البركة معه وذلك لتقليل حدوث قرحة المعدة عند هؤلاء المرضى