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RESEARCH PAPER

The anti-ulcer effect of omeprazole is modified by Nigella sativa (Black Cumin) in ethanol induced gastric ulceration in rabbits

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Abstract

Background: An interaction has been reported between Nigella Sativa (NS) and ranitidine (RAN) on gastric ulceration induced by ethanol in rabbits; the combination of NS and RAN caused disappearance of anti-ulcer effect of NS or RAN.

Objective: to investigate interaction of NS with the proton pump inhibitor omeprazole (OMP) on ethanol induced gastric ulceration in rabbits.

Methods: 24 mature rabbits were divided into 4 groups. The animals were fasted for 48 hours then divided as follow: group 1, 2, 3 and 4 were treated respectively with normal saline (orally), NS oil (10ml/kg) orally, OMP (20mg/kg) by intraperitoneal (IP) injection, and NS+ OMP. One hour later, animals were given absolute ethanol orally; and sacrificed 3 hours later for estimation of Ulcer index (UI), gastric pH, malondialdehyde (MDA), glutathione (GSH) and histamine (HIS) concentrations in serum and gastric tissue.

Results: Ethanol induced gastric ulceration in all animals with an UI of 10 ± 0.11 mm^2. This effect was paralleled with reduction in gastric pH, increased MDA and HIS and reduction in GSH. UI was reduced to 5.13 ± 0.68 mm^2 in NS group, P value = 0.07 and to around zero in OMP group. NS or OMP treatment resulted in reduction in serum and tissue MDA and HIS concentrations and increased in GSH and gastric pH levels. In NS + OMP treated group, UI became higher than OMP group with MDA and HIS tended to rise and GSH and gastric pH declined.

Conclusion: NS + OMP diminished the gastro-protective effect of either NS or OMP.

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Introduction

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[1,2], these effects were largely attributed to its antioxidant potential. [3] As reported with many drugs, herb-drug interactions were widely studied and considered as a serious problem which may adversely affect patient's health.[4,5] There were numerous studies documenting an interaction between NS and some drugs such as sildenafil[6], phenytoin[7], cyclosporine [8], losartan [9] with a reduction in the area under the concentration time curve (AUC), Cmax, and bioavailability. On the contrary, an increase in the (AUC), Cmax and bioavailability of amoxicillin were observed when concomitantly administered with NS. [10]

In a previous study, Ahmed and colleagues[11] had reported an interaction between NS and ranitidine in a rabbit model of alcohol induced gastric ulceration; the study showed that the observed antiulcer effect with either NS or ranitidine was considerably decreased when the two agents were given together. The mechanism behind this interaction was not known. To explore the nature of such interaction, an antiulcer drug with different mechanism of action has been suggested for investigation. Omeprazole was chosen and the study was designed to investigate the effect of NS or omeprazole alone and in combination on ethanol induced gastric ulceration in rabbits.

Methods

The study protocol was approved by the Ethical Committee of the College of Medicine, University of Basrah and carried out between November 2017 and May 2018

Preparation of NS and OMP

NS seeds were purchased from a local market, authenticated by a special botanist and a sample of the seeds was kept in the Department of Pharmacology for future reference. The oil of NS was extracted by a cool press extraction technique with a yield of 25% of the oil. The oil was collected and stored in a clean container at room temperature.

OMP (Strides Pharma, India) is available as a vial containing 40 mg powder. The powder was reconstituted in normal saline to obtain a concentration of 10 mg/ml of OMP.

Animal handling

Twenty four sexually mature male and female locally breed rabbits weighing between 0.9 – 1.4 kg were chosen for the study. The rabbits were kept for 7 days in separate cages in the animal house of the College of Medicine for acclimatization at a dark/light ratio of 12/12 h and temperature at 25^{o}C with free access to water and food. The animals were then divided into 4 groups; 6 animals in each group (three males and three females). The rabbits were transferred into separate restrain cages with a special piece of wood (neck restrain) which kept the head of the animal outside the cage away from its droppings to ensure complete fasting condition. At the end of 48 h of restrain, the animals were treated according to the study design (Table 1). NS or any orally administered substance were given by a pediatric nasogastric tube fixed into a syringe. The dose of NS was introduced into the stomach of the rabbit through a wooden tongue depressor with a hole in the middle to prevent the rabbit from chewing the tubes. OMP was given by intraperitoneal route (IP) using insulin syringes. All treatments were given as single doses. Two animals from each group were studied at a time

Table 1. Study design (n= 6 rabbits in each group)

Treatment groups	0 time (treatment)	1 hour after treatment	3 hours after ethanol
Group 1: Ethanol treated group	10ml/kg normal saline (oral)+2.5 ml/kg normal saline (I.P)	5ml/kg absolute ethanol (oral)	Animals were sacrificed
Group 2: Nigella sativa oil	10ml/kg Nigella sativa oil (oral) + 2.5 ml/kg normal saline (I.P)	5ml/kg absolute ethanol (oral)	Animals were sacrificed
Group 3: Omeprazole	20 mg/kg Omeprazole (I.P) + 10ml/kg normal saline (oral)	5ml/kg absolute ethanol (oral)	Animals were sacrificed
Group 4: Nigella sativa + Omeprazole	10ml/kg Nigella sativa oil (oral)+ 20 mg/kg Omeprazole (I.P)	5ml/kg absolute ethanol (oral)	Animals were sacrificed

Omeprazole, Nigella sativa and the combination were given as single doses

Three hours after ethanol administration, the animals were transferred to a glass jar containing a piece of cotton soaked in chloroform. After light anesthesia, 5 ml of blood was collected directly from the heart. The rabbits were then returned back to the anesthetic jar to receive deep anesthesia to ensure painless sacrifice.

Preparation of the stomach

Immediately after death of the animal, the abdomen was opened; stomach was ligated at the two ends and removed. The stomach was then opened along the greater curvature; the contents were collected, centrifuged at 5000 RPM for 5 minutes. The supernatants were collected for measurement of gastric pH using a small pen-like digital pH meter (Semlose, Poland). The inner surface of the stomach was gently washed with a clean tap water for clear inspection of gastric mucosa. A piece (1g) of tissue was taken from the edge of the ulcer areas for biochemical measurements of (MDA, GSH, and His) and a piece of the tissue was placed in 10% formalin for histopathological examination.

Measurement of ulcer index

Ulcer index (UI) was measured by an ordinary ruler with a help of a magnifying lens. Ulcer index was defined as a summation of total ulcer lengths (in mm) for all animals divided by the number of animals in that group.[12] Five hemorrhagic spots were counted equivalent to 1mm of ulcer.[13]

Collection and storage of samples

Blood samples were allowed to clot at room temperature for 2 h, centrifuged at approximately 5000 RPM for 20 min. The supernatants were stored in Eppendorf tubes at -20°C till the time of analysis.

For the preparation of tissue homogenate, one gram of gastric tissue was taken from ulcerated areas, minced to small pieces, placed in a small glass container. Nine milliliters of phosphate buffer saline (pH 7.4) were added to the container to obtain a 10% tissue homogenate. The small glass container was placed in a large glass container filled with ice to prevent rise of homogenate temperature during homogenization. The stomach tissue was homogenized using mechanical homogenizer (Heildolph, Germany) at 5000 RPM for 5 min. The supernatant was collected and stored at -20°C till the time of analysis.

Biochemical measurements

Estimation of MDA concentration in serum and gastric tissue homogenate

MDA concentrations, both in the serum and in gastric tissue homogenate were measured by Competitive-ELISA detection method (ELISA reader & washer, Biotek, Germany) using a special kit for rabbits (MyBioSource, china). Color changes obtained from this procedure was estimated spectro-photometrically at 450 nm wavelength. MDA concentration was inversely proportional to color intensity in the sample.

Estimation of GSH concentration in serum and gastric tissue homogenate

GSH concentrations were measured in the serum and gastric tissue homogenate using competitive-ELISA detection method using a kit for rabbits (MyBioSource, china).

Estimation of HIS concentration in serum and gastric tissue homogenate

ELISA competitive method was used for measurement of HIS concentrations using a special kit for rabbits (MyBioSource, china).

Histopathological Examination

A piece of stomach tissue from the ulcer area was taken, transferred to a tube containing 10% formalin for histopathological examination. This test was performed on two animals from each group.

Statistical analysis

SPSS version 15 was used for statistical analysis. One way analysis of variance

(ANOVA) was used for data analysis. Unpaired t-test was used for comparing differences between the means. P-values less than 0.05 are accepted as statistical significance. The data were presented as mean ± standard deviation.

Results

There were no differences between males and females regarding the studied parameters.

Effect of NS, OMP and their combination on gastric ulcer

Treatment with NS decreased the UI from a mean value of 10 ± 5.50 mm^2 in the ethanol treated group to 5.13 ± 1.42 mm^2 in NS treated group, however this reduction did not achieve statistical significance (P = 0.07). OMP treatment achieved near complete inhibition of gastric ulceration with a mean UI of 0.67 ± 1.21 mm^2 which was significantly lower than that obtained with the ethanol treated group (P = 0.002) and NS treated group (P = 0.001). The mean value of UI significantly increased towards the ethanol treated group in the animals treated with the combination OMP + NS to a level which was significantly higher than treatment with OMP separately (P = 0.018), (Table 2).

Effect of NS, OMP and their combination on gastric pH.

NS or OMP treatment significantly increased gastric pH from a mean value of 2.05 ± 0.11 in the ethanol treated group to 3.12 ± 0.67 (P = 0.004) and 5.79 ± 0.94 (P = 0.001) in NS and OMP treated group respectively, while the pH value of the treatment with NS + OMP tended to decline to 3.82 ± 0.25 which was significantly lower than OMP treated group (P = 0.001), (Table 2).

Table 2. Effect of NS, OMP, and their combination on alcohol induce gastric ulcer and gastric pH in rabbits

Treatment	UI mm^2	pH
Ethanol treatment	10 ± 5.50	2.05 ± 0.11
NS + Ethanol	5.13 ± 1.42 (a)	3.12 ± 0.67 (d)
OMP + Ethanol	0.67 ± 1.21 (b)	5.79 ± 0.94 (e)
NS+OMP + Ethanol	1.68 ± 1.14 (c)	3.82 ± 0.25 (f)

NS: nigella sativa, OMP: omeprazole, UI: ulcer index

(a) : marginal significantly lower than the ethanol treated group (P = 0.07).

(b) : significantly lower than the corresponding value of the ethanol treated group (P = 0.002) and NS (P = 0.001); (c): significantly higher than OMP treated rabbits (P = 0.018); (d); significantly higher than the ethanol treated group (P = 0.004); (e) : significantly higher than the ethanol treated group (P = 0.001) and NS (P = 0.001); (f): significantly lower than OMP treated rabbits (P = 0.001). Data are presented as mean ± SD.

Effect of NS, OMP and their combination on MDA concentration in gastric tissue homogenate

Both NS and OMP decreased stomach tissue MDA concentration when given separately (41% and 19% respectively) compared to ethanol treated group, these changes did not achieve statistical significance. But when the two treatments were combined (NS + OMP), the concentration of tissue MDA increased and only achieved statistical significance compared to NS treatment (P = 0.027), (Table 3).

Effect of NS, OMP and their combination on serum MDA

NS and OMP treatments, when given separately significantly reduced serum MDA concentration compared to ethanol treated group (46% and 32% respectively); this achieved statistical significance (P = 0.002 and P = 0.041 for NS and OMP respectively). But treatment with the combination (NS + OMP) significantly increased serum MDA concentration to levels higher than either NS or OMP treatments, however, statistical significance was achieved with NS treatment only (P = 0.031), (Table 3).

Effect of NS, OMP and their combination on GSH concentration in gastric tissue homogenate

NS and OMP treatments increased gastric tissue GSH concentration (9% and 77% respectively) but statistical significance was achieved only with OMP treatment compared to ethanol treated group (P = 0.033). While, the rise in gastric tissue GSH concentration observed with NS or OMP treatment separately tended to decline from 4.2 ± 2.6 in NS group or 6.7 ± 1.8 in OMP group to 4.0 ± 1.6 in the combination (NS + OMP) with a statistical difference achieved between the combination and OMP treatment, (P = 0.021) (Table 3).

Effect of NS, OMP and their combination on serum GSH concentration

NS and OMP treatments increased serum tissue GSH concentration (33% and 22%), both achieved statistical significance compared to the ethanol treated group (P = 0.008 and P = 0.016 respectively). There was a small and statistically insignificant change in serum tissue GSH concentration in the group treated with the combination compared to either NS or OMP treatments (Table 3).

Effect of NS, OMP and their combination on HIS concentration in gastric tissue homo genate

Treatment with NS or OMP when administered separately decreased tissue HIS concentration (40% and 32% respectively) compared to the ethanol treated group; these reductions were statistically significant for NS (P = 0.001) and for OMP (P = 0.002). The concentration of tissue HIS elevated in the group treated with the combination NS + OMP which achieved statistical significance compared to NS treated group only (P = 0.04), (Table 3).

Effect of NS, OMP and their combination on serum HIS concentration

Both NS and OMP when given separately decreased serum concentration of HIS (20% and 7% respectively), but statistical significance was achieved with NS treatment only compared to the ethanol treated group (P = 0.001). The serum concentration of HIS rose in the combination treated group compared to NS or OMP treatments, but statistical significance was

achieved with NS treatment only (P = 0.037), (Table 3).

Table 3. Effect of NS, OMP, and their combination on MDA, GSH and HIS concentration in serum and gastric tissue homogenate in rabbits

Treatment	Tissue MDA (ng/ml)	Serum MDA (ng/ml)	Tissue GSH (ug/ml)	Serum GSH (ug/ml)	Tissue HIS (ng/ml)	Serum HIS (ng/ml)
Ethanol treatment	91.6 ± 60.3	120.17 ± 30.8	3.81 ± 2.25	83.66 ± 9.77	10.6 ± 1.9	390 ± 23.5
NS + Ethanol	53.8 ± 2 (41%)	65.4 ± 5.2 [b] (46%)	4.2 ± 2.6 (9%)	111.6 ±18.2[g] (33%)	6.3 ± 1.4[i] (40%)	311.5 ± 27.2[l] (21%)
OMP + Ethanol	74.5 ± 24.9 (19%)	82.3 ± 24.7 [c] (32%)	6.7 ± 1.8[e] (77%)	102.3 ± 12.4[h] (22%)	7.1 ± 0.8[j] (32%)	362.3 ± 54 (7%)
NS+OMP + Ethanol	83.7 ± 20.8[a]	99.8 ± 33.4 [d]	4.0 ± 1.6[f]	105.2 ± 14.1	8.6 ± 1.9[k]	373.9 ± 57.3[m]

NS: nigella sativa, OMP: omeprazole, MDA: malondialdehyde, GSH: glutathione, HIS: histamine.

(a): significantly higher than NS (P = 0.027), (**b**); significantly lower than the ethanol treated group (P = 0.002); (**c**): significantly lower than the ethanol treated group (P = 0.041); (d): significantly higher than the NS treatment (P = 0.031), (e): significantly higher than the ethanol treated group (P = 0.033), (f): significantly lower than OMP treatment (P = 0.021), (**g**): significantly higher than the ethanol treated group (P = 0.008); (**h**): significantly higher than the ethanol treated group (P = 0.016), (i): significantly lower than the ethanol treated group (P = 0.001); (j): significantly lower than the ethanol treated group (P = 0.002); (k): significantly higher than the NS treatment (P = 0.04).; (**l**): significantly lower than the ethanol treated group (P = 0.001), (**m**): significantly higher than NS treatment (P = 0.037), (%): percent change from ethanol treated group. Data are presented as mean ± SD.

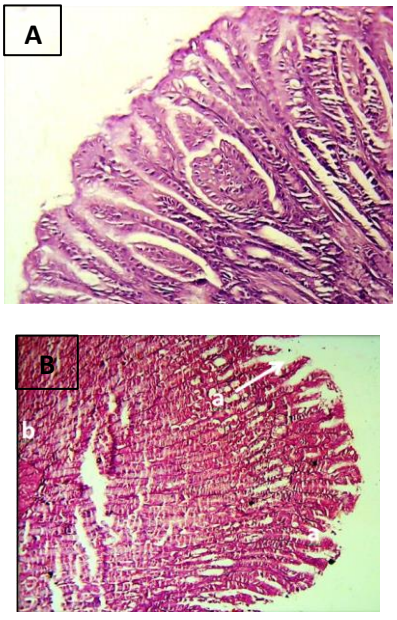
Effect of NS, OMP and their combination on histopathological examination of gastric tissue

Histopathological examinations were performed on two animals in each group. Animals were selected randomly for this test.

There were histopathological changes of gastric mucosa in the group of rabbits treated with ethanol; these changes were mucosal necrosis, atrophy and edema of deep gastric glands without inflammatory cells infiltration.

OMP treatment completely ameliorated alcohol induced gastric ulceration in the treated rabbits. Treatment with NS reduced alcohol induced gastric ulceration but to a degree less than OMP; in the NS treated group, some histopathological changes (cell infiltration) still can be seen in some parts of the mucosa particularly the uppermost superficial glandular layer, while the lower two third of the mucosa is clear of any ulceration.

In the group of rabbits treated with the combination (OMP + NS), histopathological changes in the form of superficial epithelial cells necrosis were seen in some part of mucosa. These results are presented in (Figure 1).



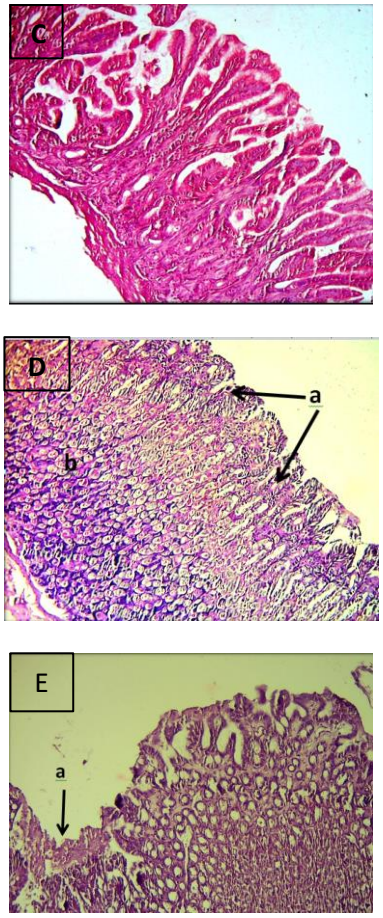


Figure 1. Representative slides of histopathological examinations of gastric mucosa (X40) in rabbits treated with: (A): normal saline revealing normal mucosa, (B): oral ethanol revealing (a): ulceration, (b): edema of deep glandular area, (C): OMP prior to oral ethanol treatment, the mucosa appeared normal, (D): NS prior to oral ethanol treatment, (a): there were mild changes (cell infiltration) in uppermost superficial layer, (b): normal glandular layer, (E): OMP + NS prior to oral ethanol treatment (a): superficial epithelial cells necrosis in some part of mucosa.

Discussion

Physicians rarely blame herbs as a cause of an unusual interaction when herbs and prescription drugs are given at the same time. The reason for that, most of physicians are not familiar with herbal medications and the possible related interactions. [14] Moreover, Physicians are influenced by the belief that if herbs are not beneficial, they will not do harm. While in fact, in many occasions, herbs may cause serious consequences. Herbal medications are usually composed of mixtures of more than one active ingredient. Hence, the possibilities of drug-herb

interactions are theoretically higher than interactions between drugs. Drugs frequently contain a single chemical constituent.[15]

These thoughts encouraged our team to conduct studies on drug interaction with NS. The first study was done to evaluate interactions between NS and ranitidine on alcohol induced ulceration in rabbit model [11], and found that, in contrast to what is expected from two gastro-protective agents (ranitidine and nigella sativa), the anti-ulcer effect disappeared when the two agents were given together. The source of interaction is not known and warrant further investigation. The present study was designed to investigate whether a similar interaction exists between NS and omeprazole, a proton pump inhibitor with a mechanism substantially different from ranitidine when the two agents are given in combination. Rabbit model of ethanol induced gastric ulceration is chosen since it can serve as more clinically relevant models as it demonstrates deep ulcers with clear margins and well-defined healing phases that was difficult to obtain in rat models. [16] Alcohol induced gastric ulcer model is widely used since many of the causative factors of gastric damage can be speculated; first: ethanol may cause direct damage to gastric endothelium [17], second: ethanol increases gastric acid secretion[18], and third: ethanol may decrease prostaglandins synthesis and secretion by gastric mucosa. [19]

NS treatment

NS oil was given orally one hour before ethanol administration to avoid dilution by ethanol when the two compounds were given at the same time and also to offer a sufficient time for absorption of NS oil in order to exert a gastro-protective effect.

NS oil significantly decreased gastric mucosal damage induced by absolute ethanol. The result of that study is in agreement with other studies [20,21,22], and thought that the antioxidant effect of NS [3] is the main factor of its gastroprotective effect.

In the present study, NS oil reduced the concentrations of parameters of oxidative stress (MDA) both in stomach tissue and in the serum and at the same time resulted in an elevation of both tissue and serum glutathione (GSH) concentrations. NS is also known to have antihistaminic effect which may act as another contributing factor for NS related anti-ulcer effect.[21] NS significantly lowered concentrations of HIS both in the serum and gastric tissue. These results are in agreement with data reported by.[21,23,24] Thymoquinone, the most active ingredient of NS has been shown to reduce peptic activity of gastric juice possibly via inhibition of the release of HIS.[21] Other mechanisms of thymoquinone gastro-protective potential include inhibition of proton pump, reduced gastric acid secretion, enhancing secretion of mucin and nitric oxide production.[22]

It is well known that HIS is involved in gastric secretions thus antihistaminic drugs which act on H2 type of HIS receptors lower gastric acid secretion and treat peptic ulcers through this mechanism. However, it is not yet known whether the antihistaminic effect of NS involves H1 or H2 HIS receptors.

Another mechanisms were reported by other researchers explaining the anti-ulcer effects of NS; these are:

1. NS oil may contribute to the releasing of endogenous prostaglandins which may play a physiological role in protection of

gastric mucosa by maintaining cellular integrity of the gastric epithelium.[25]

2. NS is reported to cause marked inhibition of the release of leukotrienes which may lead to mucosal tissue hypoxia and injury.[26]As a result, it may alter the balance between prostaglandins and leukotriens in gastric mucosa towards cytoprotection.

3. NS formed protective complexes with mucus that may act as a barrier against several necrotizing agents.[22,25]

OMP treatment

Treatment with OMP produced a significant reduction in UI (more than 90%). This could simply be expected from a proton pump inhibitor drug like OMP. OMP significantly elevates gastric pH to levels higher than that observed with the ethanol treated group or NS treated group. Another observation was that OMP causes reduction of both gastric and serum levels of MDA compared to the ethanol treated group. This effect is paralleled with an elevation of GSH in gastric tissue and the serum. These observations signify that OMP could have antioxidant properties. This result is consistent with other studies which showed that OMP has anti-oxidant properties [27,28] which may be considered as contributory factor for OMP therapeutic effects.

Treatment with OMP significantly reduced tissue HIS and to a lesser extent serum HIS concentrations compared to the ethanol treated group. Reduction of HIS in gastric tissue does not exactly imply that OMP has antihistaminic effect. On the contrary, this may indirectly result from prevention of ethanol induced stress leading to amelioration of gastric ulceration which ultimately results in reduced HIS release.[29]

Combination of NS + OMP

The combination OMP + NS caused reversal of all measured parameters; the anti-ulcer effect of OMP or NS regressed towards the ethanol treated group as documented by increased ulcer index in the group treated with the combination. Similarly, gastric pH tended to decline with the combination treatment.

Although the mechanism behind this interaction is not well known but at least, it could have a clinical significance. Reduction in the anti-ulcer effect of OMP by NS could result in therapeutic failure when NS is added to an anti-ulcer regimen containing OMP. Serum and gastric tissue MDA rose towards the ethanol treated group with the combination of treatment after being reduced by NS or OMP treatment separately. GSH declined with the combination treatment. These results may suggest that oxidative stress may play a key role in this interaction. In one study, NS is generally described as an antioxidant but in certain cell or organ, acts as pro-oxidant.[30] It can be speculated that NS may act as pro-oxidant in situation where interaction with OMP is involved. Effect on serum and gastric tissue HIS may provide an additional explanation of the interaction between OMP and NS. The concentration of HIS tended to rise in the group treated with the combination after being reduced by NS or OMP when given separately. Rise in HIS concentration in the group treated with the combination may stimulate acid secretion and increase gastric ulceration. These findings were also supported by the histopathological examination which revealed that gastric ulceration increased in the group treated with the combination.

Both OMP and NS share the same metabolic pathways in the liver, and cytochrome CYP2C19, CYP3A4 and CYP2D6[31] are involved in the metabolism of the two agents. Therefore, an interaction between OMP and NS with reduction in OMP plasma concentration cannot be ruled out.

OMP is a prodrug[32] which needs to combine with acid in the canaliculus of the parietal cell for activation. NS decreased gastric acidity, leading to decreased protonation of OMP with decreased activation of OMP and reduced activity.

Herbal-drugs interaction may be either pharmacokinetic or pharmacodynamics. In the current study, NS was given orally and OMP was given by intraperitoneal route; this at least excludes an interaction between NS and OMP at the sites of absorption from gastrointestinal tract.

Conclusion

Combination of NS with OMP diminished the gastro-protective effect produced by monotherpy of NS or OMP. At this stage, combination of OMP with NS may be discouraged for the treatment of peptic ulcer in human.

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تخفيف فعل الاوميبرازول المانع لقرحة المعدة بواسطة الحبة السوداء (الكمون الأسود) فى القرحة المعدية المحدثة بالإيثانول فى الارانب

خلفية الدراسة: اظهرت إحدى الدراسات تداخلاً بين الحبة السوداء والرانتدين على تقرح المعدة الناجم عن الايثانول فى الارانب .وكانت نتيجة تلك الدراسة اختفاء فعل الرانتدين المانع للقرحة المعدية عند اعطائه مع الحبة السوداء
.الهدف: لتقصى تأثير تداخل الحبة السوداء مع الاومبرازول على القرحة المعدية الناجمة عن الايثانول فى الأرانب
طرائق العمل: تم تقسيم 24 ارنباً الى أربع مجموعات حيث منعت الحيوانات عن الطعام لمدة 48 ساعة ثم عولجت المجموعات 4،3،2،1 على التوالى باستعمال المحلول الملحى العادى (عن طريق الفم) وزيت الحبة السوداء (10 مل/كغم عن طريق الفم)

والاومبرازول (20 ملغم/كغم) عن طريق الحقن البريتونى والاومبرازول وزيت الحبة السوداء معا". وبعد ساعة واحدة أعطيت الحيوانات الايثانول المطلق عن طريق الفم وتم التضحية بالحيوانات بعد 3 ساعات لقياس مؤشر القرحة، ودرجة حموضة المعدة، والمالوندايلديهايد، والكلوتاثيون والهستامين فى مصل الدم وأنسجة المعدة.

النتائج: ظهرت تقرحات المعدة فى جميع الحيوانات التى اعطيت الايثانول وبمعدل مؤشر للقرحة يساوى 10 ± 0.11 ملم2 وتزامن هذا التاثير مع انخفاض درجة حموضة المعدة وزيادة مستويات المالوندايلديهايد والهستامين وانخفاض فى مستوى الكلوتاثيون. وقد انخفض موشر القرحة الى 5,13 ± 0.68 ملم2 فى المجموعة التى عولجت بالحبة السوداء (قيمة الاحتمال = 0.07)، والى درجة صفر فى المجموعة التى عولجت بالاومبرازول. كما أدت المعالجة بالحبة السوداء او بالاومبرازول الى انخفاض مستويات مالوندايلديهايد والهستامين وزيادة فى الكلوتاثيون فى مصل الدم وفى الانسجة وارتفاع فى درجة حموضة المعدة. أما المجموعة التى عولجت بالاومبرازول وزيت الحبة السوداء معاً، فقد ارتفع مؤشر القرحة بدرجة أعلى مما أحدثه الاومبرازول بمفرده مع ارتفاع فى مستويات مالوندايلديهايد والهستامين وانخفاض فى مستوى الكلوتاثيون ودرجة حموضة المعدة.

الاستنتاج: إن إعطاء زيت الحبة السوداء والاومبرازول معا" أدى الى خفض الفعل المانع للقرحة الناتج عن المعالجة بالاومبرازول أو زيت الحبة السوداء كلّ على حدة.