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Research Article

The Effect of Cumin Essential Oil on the Changes in Total Oxidant Status and Interleukin-6 in the Model of Gastric Ulcer in Rats

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Abstract

The role of oxidative stress and interleukin-6 as well as calcium in the pathogenesis of gastric ulcer is controversial. The antioxidant, anti-inflammatory, and antimicrobial properties of cumin in the gastrointestinal disease has been investigated. In this experimental study, the effect of cumin essential oil on the serum changes of these factors was investigated. The study was conducted on 6 groups of rats as follows: Group 1: Sesame oil (as cumin diluent), Group 2: Cumin essential oil 400 mg/kg, Group 3: Indomethacin at the dose of 50 mg/kg, Group 4: Indomethacin 50 mg/kg + Cumin essential oil 200 mg/kg, group 5: indomethacin 50 mg/kg + Cumin essential oil 400 mg/kg, group 6: indomethacin 50 mg/kg + omeprazole 20 mg/kg. All drugs received orally. After 6 hours of indomethacin administration, rats were anesthetized with ketamine-xylosin. Blood was collected via cardiac puncture after euthanasia. Total Oxidant Status (TOS) and interleukin-6 (IL-6) were measured in serum using a commercial ELISA kit and total serum calcium was analyzed with auto analyzer. Indomethacin caused the destruction of the covering epithelium and the invasion of inflammatory cells and also induced microscopic edema of the stomach tissue and caused a significant increase in interleukin 6 in the serum of rat. Cumin in both doses of 200 and 400 mg reduced tissue damage and decreased IL-6 significantly ($p < 0.05$). Indomethacin significantly increased Total Oxidant Status (TOS) compared to cumin group alone ($p < 0.05$). The amount of serum calcium in the group receiving indomethacin + omeprazole was significantly lower than the other groups, and the average of this factor was not statistically different among the other groups, in other words, indomethacin and cumin essential oil had no effect on the amount of serum calcium. Indomethacin significantly increased IL- 6 and TOS and had no effect on calcium levels. Cumin essential oil decreased only the amount of IL-6 significantly.

Introduction

Peptic ulcer disease is related to imbalance between inflammation and mucosal defends include prostaglandin production, bicarbonate production and peripheral blood circulation. Many factors accelerate ulcer such as smoking, stress, NSAID, H-pylori infection and so on. There are many drugs to treat peptic ulcer disease including PPI, H2blockers and antibiotics. On the other hand new methods in the treatment of peptic ulcer disease effectively has been found.

Some studies showed that free radicals have important roles in development of peptic ulcer disease. Therefore, antioxidants may be effective in the treatment of peptic ulcer disease. In some studies it was shown that Cumin seeds have anti-inflammatory properties as well as antioxidant effects. Also it could scavenger free radicals that related to its antiulcer effects [1]. Recent investigations have further supported the gastroprotective, anti-inflammatory, and antioxidant properties of cumin and other plant-derived compounds in gastrointestinal disorders [2-4].

Reactive Oxygen Species (ROS) involves in the pathogenesis of some diseases such as peptic ulcer disease induced by ethanol. Enzymatic and non-enzymatic cellular antioxidants defenses such as CAT, SOD, GPx, and GSH has protective effects against oxidative stress [5].

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Cuminum Cyminum is a plant that grows in many countries and contains tannin, oleoresin, essence and flavonoid and its main active material is cumminic aldehyde that is 63% of its whole active material. Vader, et al. showed that hydro alcoholic extract of cumin has gastro intestinal mucosal protective effect in diabetic rats [6]. It also increases cellular antioxidant defenses. IL-6 is a cytokine that its level in the blood is increased temporarily after infection and also its concentration is increased after tissue damage and increased through activation the acute phase response and after erythropoiesis and immune system activation also IL-6 strengthens host immune system defenses [7] also its expression is controlled by some transcription factors [7]. On the other hand, its irregular production has pathologic effects and increase inflammation and autoimmune reactions [7]. Peptic ulcer disease is relative to imbalance between acid secretions and mucosal defends. On the other hand stomach and duodenal cells secrete bicarbonates that buffers acids of gastrointestinal tracts also prostaglandin E2 is an important role in mucosal defends. It increases bicarbonate secretion and mucosal layers [8]. On the other hand, NSAIDS and H Pylori infection, ethanol consumption and bile acid salts can impair mucosal defenses. H pylori is a gram negative bacteria and its relation to peptic ulcer disease was approved at first in 1983.Terefore three factors include acid, pepsin and H-pylori infection have important role in peptic ulcer production [8]. *Cuminum Cyminum* is an annual plant from Apiaceae family that is native in Mediterranean countries also cultivated in Mexico and China and India [9]. Cumin has some nutritive and therapeutic effects and used as an antispasmodic and for menstrual disorders and also has diuretic and anti-swelling effect and used for abortion [9]. Cumin increase breast milk and used as anti-gastritis and anti-cancer [9]. As well as it used as medicinal food in the diabetes treatment [9].

Materials and methods

Drugs and biochemical reagents

Indomethacin and Omeprazole were purchased from Longman Pharmaco-Company Iran. Cumin essence were purchased from Barij Essence Company Iran. IL6-Elisa Kit (CN: KPG-RIL6 -96), KPG- RIL6 S4, OD: 2.4 – 022 (pictogram/ml) purchased from Karenina Pars Gen .Iran. Ketamine Hydrochloride 10% were purchased from Alfasan Netherlands. Xylosin 2% was purchased Alfasan Netherlands.

Animal

Adult male Wister rats taken from animal house of Babol University of Medical Science of Iran weighing between 200–220 g were used in this study. The Animals were housed at 22°C in a controlled environment with a12:12 hour light: dark cycle and were given access to standard laboratory food and water ad libitum. All experiments were carried out in accordance with the Guide for the Care and Use of Laboratory Animals (National Institutes of Health Publication No. 80-23, revised1996) and were approved by the Research and Ethics Committee of Babol University of Medical Science. Ethical ID: IR.MUBABOL.AEC.1402.002. Animals were divided into 6 groups of 5 male rats in each groups. Group 1: Sesame oil (as cumin diluent), Group 2: Cumin essential oil 400 mg/kg, Group 3: Indomethacin with a dose of 50 mg/kg, Group 4: Indomethacin 50mg /kg + Cumin essential oil 200 mg/kg, group 5: indomethacin 50 mg/kg + Cumin essential oil 400 mg/kg, group 6: indomethacin 50 mg/kg + omeprazole 20 mg/kg and all drugs received orally. All rats were fasted for 24 hours prior to drug administration. After 6 hours of drugs administrations rats were anesthetized with ketamine-xylazine and blood was collected from the hearts of rats and referred for biochemical analysis.

Total Oxidant Status (TOS) and IL-6 in serum of rat blood were assayed by IL6-Elisa Kit (CN: KPG-RIL6 -96) and Total serum calcium was analyzed with auto analyzer. Absorbance was measured at 450 nm using a microplate reader after 20 minutes of substrate incubation at room temperature. Also histological analysis were done with H & E staining and examined under an optical microscope. All data analyzed statistically with one way ANOVA and Post Hoc test with SPSS software (version 19). All results in p value < 0.05 were known as significant and shown as Means ± SEM.

Results

Histopathological analysis

Slices derived from the stomach were stained with H&E and histological studies showed that the inflammation and destruction in the cell layers of gastro mucosal membrane with and immune cells migration to the damaged tissues were induced by indomethacin administration. By the use of cumin 200 mg/kg, epithelium damages were decreased and by the use of cumin 400 mg/kg no damage was seen. Also by the use of omeprazole, the damage of epithelium cells were decreased and the migration of immune cell and inflammation were diminished.

IL-6 assay

In the serum of rats in Indomethacin group, the concentration of IL-6 was 22.68 ± 2.09 Nano mole/ml. and in sham group that received oleoresin. IL-6 concentration was 15/03 ± 0/66. Nano mole/ml. There was a significant difference between Indomethacin groups with all of groups except Omeprazole group (Figure 1). Therefore cumin extract (400 mg/kg) decrease IL- 6 concentration significantly. ($p < 0.05$) (Figure 1). In Indomethacin and omeprazole group the level of IL-6 is higher in comparison with resin groups, ($p < 0.05$) (Figure 1). Therefore, In Cumin groups, at the dose of 200 and 400 mg/kg the level of IL-6 decreased significantly, ($p < 0.05$) (Figure 1).

Oxidative stress

The concentration of H_2O_2 in serum of rat was considered as total oxidative status (TOS). H_2O_2 level in Cumin 400 mg/kg + Indomethacin 50 mg/kg was high (75/26 ± 5/27) nanomol /ml. The H_2O_2 level in Omeprazole 20 mg/kg + Indomethacin 50mg/k was low (20/12 ± 4/07). In Cumin Group there was a significant difference with all groups except omeprazole group ($p < 0.048$).

(Figure 2). Cumin at the dose of 200 mg/kg decreased H_2O_2 levels in comparison with resin group. (Figure 2). Omeprazole could decrease H_2O_2 levels significantly, ($p < 0.05$) (Figure 2).

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Serum calcium assay

The level of calcium in oleoresin and Cumin 400 mg /kg + Indomethacin 50 mg/kg groups were high (11.4 mg/dl) and this level in Indomethacin 50 mg/ kg + Omeprazole 20 mg/kg was low (5/93 ± 0/81 mg/dl). There were no significant difference between the other groups (Figure 3).

Discussion

In this research we found that indomethacin could induce inflammation and destruction in protective mucosal layer in rat's stomach also increased IL_6 concentrations in the serum of rats significantly ($p < 0.05$). Cumin at the dose of 200 and 400 mg/kg decreased the inflammation and destruction of mucosal layer in rat's stomach and decreased IL-6 significantly in the serum of rat ($p < 0.05$). Omeprazole 20 mg/kg decreased mucosal destruction partially, but could not decrease IL-6 level significantly ($p < 0.05$). TOS (H_2O_2) was higher in Indomethacin + Cumin 400 mg/kg than other groups but cumin at the dose of 200 mg/kg decreased H_2O_2 levels significantly TOS levels were low in both the Cumin group and the Indomethacin + Omeprazole group. Indomethacin increased TOS in all of groups in comparison with Cumin groups. Calcium concentration in Indomethacin + Omeprazole group was lower than all of groups significantly ($p < 0.05$).Also indomethacin and Cumin has no effect on the level of calcium in serum of rats. There was an increase in the level of TOS and IL-6 with indomethacin compared with each other groups. Cumin at the dose of 200 mg/kg significantly reduced H_2O_2 levels compared to indomethacin group, indicating antioxidant activity. At 400 mg/kg, cumin showed histological protection but did not cause a statistically significant reduction in TOS. Omeprazole, however, significantly reduced TOS levels. In the other studies an increase in inflammation and oxidative stress and apoptosis in gastro mucosal layers were reported with indomethacin also an increase in TOS was reported too [10,11]. In our study, indomethacin alone had no effect on calcium levels, but in combination with omeprazole, it significantly decreased calcium concentration. This may be related to the physiological effect of omeprazole on calcium concentration. Omeprazole also possesses antioxidant properties by blocking free radicals such as hydroxyl radicals (OH), inhibiting apoptosis, inducing NADPH oxidase-reductase, and increasing intracellular antioxidant capacity [12]. On the other hand Some in vivo and in vitro studies have shown that omeprazole, through TNF-α activation and modulation of IL-1β and other pro-inflammatory cytokines, may inhibit tissue necrosis [12]. Omeprazole at 20 mg/kg exerts antioxidant effects via SOD activation, while doses of 30 and 40 mg/kg activate GPx [12]. Also Omeprazole modulates ethanol-induced gastritis in rats by its anti-inflammatory and antioxidant properties [12]. Although both cumin essential oil and omeprazole demonstrated protective effects against indomethacin-induced gastric damage, their mechanisms of action appear to differ. Cumin's gastroprotective effect is primarily attributed to its antioxidant and anti-inflammatory properties, including free radical scavenging, modulation of cytokine production (notably IL-6), and enhancement of endogenous antioxidant defenses such as glutathione and superoxide dismutase. Conversely, omeprazole, a proton pump inhibitor, primarily reduces gastric acid secretion, indirectly minimizing mucosal injury, while also exhibiting antioxidant effects through inhibition of hydroxyl radical formation, NADPH oxidase modulation,

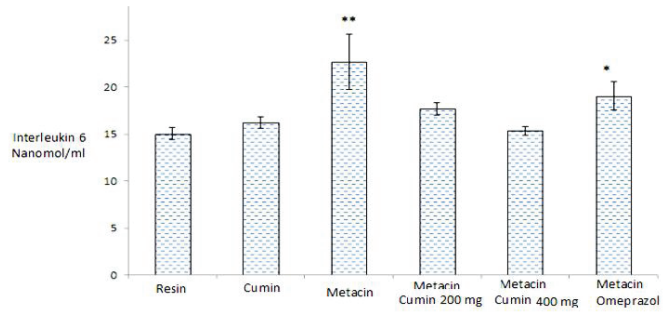

Figure 1: IL-6 concentration in experimental groups, measured with ELISA Kit (CN: KPG-RIL6-96). There is a significant difference between indomethacin groups and other groups ($p < 0.05$). *Data are expressed as Mean ± SEM ($n = 5$ per group). Statistical analysis was performed using one-way ANOVA followed by post hoc tests. $p < 0.05$ was considered statistically significant.

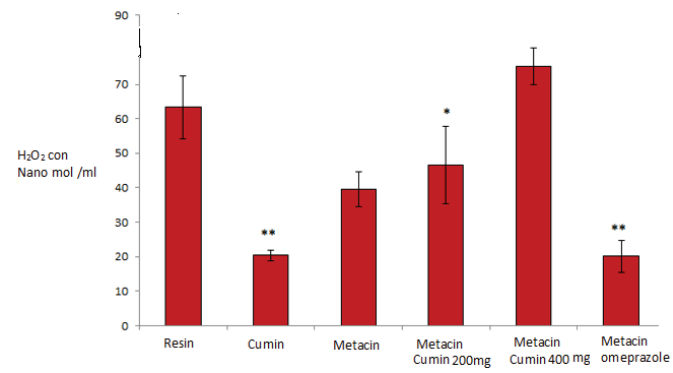

Figure 2: H_2O_2 concentration (nmol/ml) in experimental groups (each group includes 5 rats). There is a significant difference between indomethacin and resin groups, and between omeprazole + indomethacin and indomethacin groups ($p < 0.05$). *Data are expressed as Mean ± SEM ($n = 5$ per group). Statistical analysis was performed using one-way ANOVA followed by post hoc tests. $p < 0.05$ was considered statistically significant.

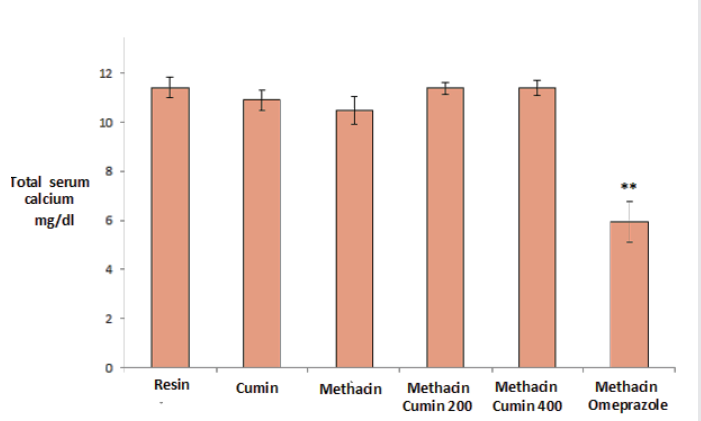

Figure 3: Total serum calcium in experimental groups. There is a significant difference between Indomethacin 50 mg/kg and Omeprazole 20 mg/kg with other groups ($p < 0.05$). Omeprazole decreased calcium levels significantly. *Data are expressed as Mean ± SEM ($n = 5$ per group). Statistical analysis was performed using one-way ANOVA followed by post hoc tests. $p < 0.05$ was considered statistically significant.

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and activation of antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx). Thus, cumin may provide a complementary antioxidant pathway alongside the acid-suppressive action of omeprazole. In our study Indomethacin increased IL-6 significantly ($p < 0.05$). IL-6 is an inflammatory cytokine that has important role in the acute and chronic inflammation and produces acute phase proteins and plays an important role in the transition from acute to chronic inflammation and continue inflammatory responses in chronic phase [12]. Khalaf, et al. showed that IL-6 increased in the model of peptic ulcer induced by indomethacin in rats [13]. We suggest that indomethacin increases IL-6 and TOS levels in rat serum, but has no significant effect on serum calcium levels in the experimental groups. On the other hand Cumin could decrease IL_6 significantly ($p < 0.05$). Vader, et al. showed that hydro alcoholic extract of cumin has gastro intestinal mucosal protective effect in diabetic rats [6] also increase cellular antioxidant defenses. Therefore antioxidant property of cumin could decrease inflammation and may scavenger free radicals and may have an important role in the treatment of peptic ulcer disease. Further comprehensive studies are required to establish the pathophysiological role of IL-6 in peptic ulcer disease and clinical trials are needed to investigate the role of natural antioxidants such as cumin essential oil in the treatment peptic ulcer disease.

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