Effects of Saffron and its Active Constituents, Crocin and Safranal, on Prevention of Indomethacin Induced Gastric Ulcers in Diabetic and Nondiabetic Rats

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Received: 14 Mar. 2009 **Accepted:** 20 Jun. 2009

Abstract

Background: Saffron is the dried stigmata of the flowers of saffron (*Crocus sativus* L., Iridaceae). Saffron is well known for the treatment of gastric disorders in traditional medicine.

Objectives: In the search for new potential antiulcer agents, the effects of the ethanol extract of saffron and its active constituents crocin and safranal as compared with omeprazole against gastric ulcer induced by indomethacin in non-diabetic and streptozocin diabetic rats were studied.

Methods: The effects of pretreatment with saffron extract (25, 100 or 250 mg/kg, p.o.), crocin (2.5, 5 or 10 mg/kg, p.o.) and safranal (0.25, 2, 5 ml/kg, p.o.) and omeprazole (30 mg/kg, p.o.) 30 min before administration of indomethacin (40 mg/kg, p.o. in non-diabetic rats and 15 mg/kg, p.o. in diabetic rats) on gastric lesions, increase of lipid peroxidation and decrease of glutathione levels induced by indomethacin in non-diabetic and diabetic rats were evaluated.

Results: Saffron extract, crocin, safranal and omeprazol prevented the gastric lesions, increase of lipid peroxidation and decrease of glutathione levels induced by indomethacin in non-diabetic and diabetic rats as compared with the control group ($P < 0.01$). The effects of saffron extract, crocin and safranal on the gastric ulcer index, lipid peroxidation and glutathione levels were comparable to omeprazole.

Conclusions: Saffron, crocin and safranal may prevent the gastric mucosa damage due to their antioxidant properties by increasing the gluthatione levels and diminishing the lipid peroxidation in the rat gastric mucosa.

Keywords: Saffron, Crocin, Safranal, Gastric ulcers, Diabetes mellitus, Rat

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[DOR: 20.1001.1.2717204.2009.8.29.25.6]

Introduction

Saffron is the dried stigmata of the flowers of saffron (*Crocus sativus* L., Iridaceae) and is cultivated widely in Iran, Spain, France, Italy, Greece, Turkey, India and China. In addition to being a widely used food additive, saffron is used in the traditional medicine as a eupeptic, diaphoretic, expectorant, tranquilizer, aphrodisiac, emmenagogue, abortifacient and in the treatment of hepatic disorders, flatulence, vomiting, spasm, dental and gingival pain, insomnia, depression, cognitive disorders, seizures, lumbago, cough, asthma, bronchitis, fever, colds, cardiovascular disorders and cancer. Saffron is recognized as an adaptogen in Indian ayurvedic medicine [1, 2]. Crocin, crocetin and safranal are the major active constituents of saffron [3]. Previous studies have demonstrated various pharmacological effects of saffron and its active constituents including anti-oxidant [4, 5, 6], anti-tumor [7], anti-genotoxic [8], memory and learning enhancing [9], neuroprotective [10], analgesic and anti-inflammatory [11], anti - convulsant [12], antianxiety [13], aphrodisiac [14], antidepressant [15], antihypertensive [16], hypolipidemic [17], insulin resistance reducing [18], tissues oxygenation enhancing [19], bronchodilator [20], antitussive [21], retina protective [22] and immunostimulant [23] effects.

Besides being used as analgesics, the non-steroidal anti-inflammatory drugs (NSAIDs) are being increasingly used for prevention of malignancies, stroke, pre-eclampsia, Alzheimer's disease and many other illnesses [24, 25]. However, the NSAIDs produce gastroduodenal ulcers in 25% of the users, often with bleeding and/or perforation. Amongst the various factors known to cause gastric ulcer, use of NSAIDs is the foremost [26]. Gastric mucosa of diabetic rats is more vulnerable to ulcerogens such as NSAIDs and peptic ulcers in diabetic patients are more severe and often associated with complications such as gastrointestinal bleeding [27, 28]. Adequate remedy for the NSAID-induced gastropathy has so far been elusive, despite recent advances [29]. Further the existing synthetic anti-ulcer drugs confer mild to severe side effects. Thus there is a need for more effective and safe anti-ulcer drugs. Plants are the most important source for the new drug development due to the resurgence of the interest in the use of herbal preparations. Some of the anti-ulcer drugs are known to exert their action via anti-oxidative activity [30]. Thus in view of the significant antioxidant effects of saffron and its active constituents, crocin and safranal, our aim of the present study was to assess the possible anti-ulcerogenic activity of saffron, crocin and safranal against indomethacin induced acute gastric ulceration in non-diabetic and streptozocin diabetic rats by measuring gastric ulcer index and to elucidate the role of antioxidant effects of saffron, crocin and safranal in their anti-ulcerogenic activity, gastric mucosa lipid peroxidation and reduced glutathione (GSH) levels were also measured.

Materials and methods

Plant material

The stigmas of *Crocus sativus* were collected from the lands of Ghaen in the province of southern Khorasan in December and dried in shadow followed by grinding. The identity of *Crocus sativus* was authenticated by a botanist and a voucher specimen of the plant (number 9723) was deposited in the Tehran University Central Herbarium.

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Preparation of plant extract

The stigmas were extracted with ethanol (80% V/V) by maceration for three days, and then the mixture was centrifuged. The crude extract was evaporated to dryness under reduced pressure at 40 °C.

Drugs

Crocin, indomethacin and omeprazole were purchased from Sigma, safranal from Fluka and streptozocin from Upjohn & Pharmacia. For dilution, all drugs and the extract were dissolved in physiological saline. All drugs were prepared immediately before use.

Animals

Male adult Wistar rats (225 ± 25 g) from our own breeding colony were used. Animals were maintained under standard environmental conditions and had free access to standard rodent feed and water.

Induction of diabetes

Animals were given streptozocin in a single intraperitoneal injection at a dose of 50 mg/kg. Five weeks after the injection of streptozocin, diabetic rats with fasting blood glucose levels more than 350 mg/dl were used for testing the anti-ulcer activity of the drugs.

Anti-ulcer activity

Rats were deprived of food for 48 h prior to starting the experiments but they had free access to drinking water. The animals were kept in cages with raised floors of wide mesh to prevent coprophagia and they were divided into groups of 10 diabetic or non-diabetic rats each. Gastric ulceration was induced by the administration of indomethacin suspended in 0.5% carboxymethylcellulose (CMC) in water (40 mg/kg, p.o. in non-diabetic rats and 15 mg/kg, p.o. in diabetic rats) as the ulcerogenic agent. Each group of animals was pretreated with physiological saline as control, saffron stigmas extract (25, 100 or 250 mg/kg, p.o.), crocin (2.5, 5 or 10 mg/kg, p.o.), safranal (0.25, 2, 5 ml/kg, p.o.) or omeprazole (30 mg/kg, p.o.) 30 min before the indomethacin administration. All drugs and the extract were dissolved and administered in physiological saline in a volume of 5 ml/kg.

The animals were killed 6 h after the indomethacin administration by using an overdose of chloroform. The stomachs were removed, opened along the greater curvature and washed in physiological saline. A person unaware of the type of treatment received by the animals, examined the stomachs under a 3-fold magnifier and scored the lesions as follows: 0, no pathology; 1, each pinhead ulcer spot; and 2-5, thread-like lesions of 2-5 mm length. The total number of ulcer spots divided by the number of animals gives the ulcer index [30].

Measurement of lipid peroxidation

The levels of thiobarbituric acid reactants (TBARS) in the gastric mucosa as index of lipoperoxides production were measured according to the modified method of Okawa et al. (1979) [31]. The mucosa was scraped with glass slides, weighed, and homogenized in 10 mL KCl (10 %). The homogenate was supplemented with 8.1 % sodium lauryl sulfate, 20 % acetic acid, and 0.8 % TBA, and boiled at 100 °C for 1h. After cooling, the reactants were supplemented with 2.5 mL n-butanol, shaken vigorously for 1 min, and centrifuged for 10 min at 2600 × g. Absorbance was measured in a spectro-photometer Perkin-Elmer Lambda 3 at 532 nm, and the results were expressed as nmol of malondialdehyde (MDA)/g tissue.

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Measurement of gastric mucosa GSH level

Glutathione (GSH) content (as acid-soluble sulfhydryl) of gastric mucosa was determined as described earlier [30]. Gastric mucosa was homogenized in 10 mL of 20 mM ice-cold EDTA for 40 s and centrifuged at 2000g for 10 min. Protein was precipitated with equal volume of 10% trichloroacetic acid. The supernatant (2 mL) was added to 2 mL of 0.8 M Tris-Cl, pH 9, containing 20 mM EDTA and mixed with 0.1 mL of 10 mM DTNB (5,5'–dithio-bis (2-nitro-benzoic acid) to yield thionitrobenzoic acid, which was measured at 412 nm using GSH as standard. The result was expressed as nmol of GSH/g of tissue.

Statistical analysis

The results were expressed as means ± S.D. and analyzed with the independent samples t test. $p < 0.05$ was regarded as significant.

Results

Omeprazole, saffron, crocin and safranal decreased the gastric ulcer index and lipid peroxidation but increased the gastric tissue glutathione levels at the doses used significantly as compared to the saline + indomethacin group in non-diabetic and diabetic rats ($p < 0.01$) (Tables 1 and 2).

Table 1: Effects of pretreatment with omeprazole, saffron extract, crocin and safranal on gastric ulcer index, gastric mucosa lipid peroxidation and GSH level in non-diabetic rats treated with indomethacin (40 mg/kg, p.o.). * p < 0.01 vs. saline + indomethacin. ** p < 0.01 vs. saline + saline.

Treatment (N = 10 in each group)	Dose (p.o.)	Ulcer index	Lipid peroxidation (nmol MDA/g tissue)	GSH (nmol/g tissue)
Saline + saline	-	-	110.8 ± 20.4	197.1 ± 13.6
Saline + indomethacin	-	37.3 ± 5.6	217.2±23.8**	132.3±6.8**
Omeprazole	30 mg/kg	15.2 ± 7.1 *	96.6 ± 20.1*	182.1±15.7 *
Saffron	25 mg/kg	23.1 ± 2.8 *	143.1± 12.4*	157.5±4.5 *
Saffron	100 mg/kg	14.2 ± 5.1 *	112.9± 10.2*	179.3±11.7 *
Saffron	250 mg/kg	11.3 ± 3.3 *	123.2± 18.7*	162.8±16.2 *
Crocin	2.5 mg/kg	19.5 ± 4.9 *	129.1± 14.3*	178.3±5.6 *
Crocin	5 mg/kg	10.6 ±2.8 *	92.1± 17.2*	201.9±12.2 *
Crocin	10 mg/kg	12.3 ± 3.4 *	89.6± 14.5*	192.3±8.6 *
Safranal	0.25 ml/kg	24.8 ± 3.8 *	118.6± 9.8*	162.7±17.3 *
safranal	2 ml/kg	13.2 ± 4.5 *	93.1± 11.6*	218.9±9.2 *
Safranal	5 ml/kg	11.2 ± 2.6 *	87.4± 12.8*	197.6± 14.4*

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Table 2- Effects of pretreatment with omeprazole, saffron extract, crocin and safranal on gastric ulcer index, gastric mucosa lipid peroxidation and GSH level in diabetic rats treated with indomethacin (15 mg/kg, p.o.). * p < 0.01 vs. saline + indomethacin. **p < 0.01 vs. saline + saline.

Treatment (N = 10 in each group)	Dose (p.o.)	Ulcer index	Lipid peroxidation (nmol MDA/g tissue)	GSH (nmol/g tissue)
Saline + saline	-	-	101.8 ± 15.6	224.8 ± 16.8
Saline + indomethacin	-	42.6 ± 6.7	197.2±27.1**	111.3±15.6**
Omeprazole	30 mg/kg	23.7 ± 6.2 *	82.7 ± 12.5*	189.1 ± 8.6*
Saffron	25 mg/kg	27.8 ± 7 *	111.7± 10.1*	148.4 ± 9.4*
Saffron	100 mg/kg	14.7 ± 3.7 *	88.9 ± 5.7*	165.2 ± 5.4*
Saffron	250 mg/kg	10.3 ± 6.2 *	74.3 ± 9.8*	178.5± 15.6*
Crocin	2.5 mg/kg	27.5 ± 5.1 *	101.7± 10.3*	172.1 ± 8.2*
Crocin	5 mg/kg	17.4 ± 2.8 *	74.2 ± 13.6*	201.3 ± 13.2*
Crocin	10 mg/kg	14.2 ± 4 *	65.6 ± 17.5*	192.4 ± 8.1*
Safranal	0.25 ml/kg	26.6 ± 5.2 *	89.6 ± 8.3*	168.2± 12.8*
safranal	2 ml/kg	16.7 ± 3.1 *	72.1 ± 6.6*	211.5 ± 9.7*
Safranal	5 ml/kg	12.1 ± 3.8 *	62.4 ± 7.8*	197.1± 15.1*

Discussion

The main findings of this study are as follows: (1) indomethacin has caused gastric lesions in diabetic rats at a dose (15 mg/kg, p.o.), less than half the dose used in non-diabetic rats (40 mg/kg, p.o.), in addition to increasing lipid peroxidation and decreasing glutathione levels in the gastic mucosa, (2) There is no significant differences between the ulcer indexes, lipid peroxidation and glutathione levels induced by indomethacin at the dose of 40 mg/kg and the dose of 15 mg/kg in the non-diabetic rats and diabetic rats, (3) Omeprazole (30 mg/kg, p.o.) has prevented the gastric lesions, increase of lipid peroxidation and decrease of glutathione levels induced by indomethacin in non-diabetic and diabetic rats as compared with the control group ($p < 0.01$), (4) Saffron extract, crocin and safranal have prevented dose dependently the gastric lesions, increase of lipid peroxidation and decrease of glutathione levels induced by indomethacin in non-diabetic and diabetic rats as compared with the control group ($p < 0.01$), (5) The effects of saffron extract, crocin and safranal on the gastric ulcer index, lipid peroxidation and glutathione levels are comparable to omeprazole (Tables 1 and 2).

The lower dose of indomethacin needed to induce gastric lesions in diabetic rats as compared to non-diabetic rats is in line with the fact that gastric mucosa of diabetic rats is more vulnerable to ulcerogenic agents [27, 28].

The results conform to a variety of studies in which saffron, crocin and safranal had protective effects against oxidation induced tissue injuries due to their antioxidant properties. Crocin prevented the death of the neuronally differentiated pheochromocytoma (PC-12) cells deprived of serum/glucose more effectively than α-tocopherol by inhibiting the

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formation of peroxidized lipids [32]. Crocin suppressed serum-deprivation induced death of PC-12 cells by increasing glutathione synthesis and inhibition of membrane lipids peroxidation [33]. Saffron, crocin and safranal had protective effects against lower limb skeletal muscle injury during ischemia-reperfusion by elevating total sulfhydryl contents, antioxidant capacity and decreasing malondialdehyde [34]. Safranal protected against neuronal cell death in the rat hippocampus following cerebral ischemic injury by elevating total sulfhydrl concentrations and antioxidant capacity and diminishing malondialdehyde in the hippocampus [35]. Crocin protected the rat brain against excessive oxidative damage in transient global cerebral ischemia by decreasing malondialdehyde levels and elevating gluthatione peroxidase activity [36]. Saffron had protective effects against genotoxins induced oxidative stress by increasing glutathione levels and reducing lipid peroxidation in mice [37].

Indomethacin induced gastric ulcer is a multifactorial process where reactive oxygen species (ROS) play a vital role in gastric damage either by its direct oxidative action or through apoptotic cell death. Among various ROS, H_20_2 can act as a signal transduction messenger to activate transcription factors NFκB (Nuclear Factor Kappa B) and AP-1 (Activator Protein 1) for gene expression of various inflammatory cytokines and proteases to cause cell damage. In fact, involvement of TNF-α (Tumor Necrosis Factor Alpha) and matrix metalloproteinases has been evident in indomethacin-induced gastric hypermotility and increased microvascular injury also cause ischemia to generate ROS through the mitochondrial electron transport chain. Mitochondria from gastric mucosal cells contain a highly active peroxidase to scavenge H_20_2 and protect the cells from ROS-mediated oxidative damage. Indomethacin significantly inactivates the gastric peroxidase to generate H_20_2 and H_20_2–derived $^{\cdot}OH$. Thus indomethacin significantly increases endogenous $^{\cdot}OH$ to cause oxidative damage by increased lipid peroxidation and thiol depletion [38].

In this study, omeprazole has prevented gastric lesions, increase of lipid peroxidation and decrease of glutathione level as compared to control ($p < 0.01$) which is in line with the previous studies [39, 40]. The fact that proton pump inhibitors such as omeprazole have pronounced antioxidant properties and scavenge hydroxyl radicals may explain the observed effects of omeprazole [41, 42].

In conclusion, the results of the present study suggest that saffron, crocin and safranal may prevent the indomethacin-induced gastric mucosa damage due to their antioxidant properties by increasing the gluthatione levels and diminishing the lipid peroxidation in the rat gastric mucosa. Thus further investigations concerning efficacy and safety of saffron and its active constituents in prevention of NSAID-induced gastric ulcers in humans seem to be warranted.

Acknowledgements

We are grateful to the Pharmaceutical Research Network affiliated with the Research Deputy of the Iranian Ministry of Health and Medical Education for sponsoring this study.

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