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Safety evaluation of saffron (*Crocus sativus*) tablets in healthy volunteers

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Abstract

Saffron (*Crocus sativus*) stigma tablets were evaluated for short-term safety and tolerability in healthy adult volunteers. The study was a double-blind, placebo-controlled design consisting of a 1 week treatment of saffron tablets. Volunteers were divided into 3 groups of 10 each (5 males and 5 females). Group I received placebo; groups 2 and 3 received 200 and 400 mg saffron tablets, respectively, for 7 days. General measures of health were recorded during the study such as hematological, biochemical and electrocardiographic parameters done in pre- and post-treatment periods. Clinical examination showed no gross changes in all volunteers after intervention. Saffron with higher dose (400 mg) decreased standing systolic blood pressure and mean arterial pressures significantly. Saffron decreased slightly some hematological parameters such as red blood cells, hemoglobin, hematocrit and platelets. Saffron increased sodium, blood urea nitrogen and creatinine.

This study showed that saffron tablets may change some hematological and biochemical parameters. However, these alterations were in normal ranges and they were not important clinically.

Keywords: Saffron (*Crocus sativus*); Clinical trial; Safety assessment; Human volunteers

Introduction

Crocus sativus L. stigma commonly known as saffron is a perennial stemless herb of the Iridaceae family that is widely cultivated in Iran. Commercial saffron comprises the dried red stigma with a small portion of the yellowish style attached. Compounds considered pharmacologically active and important are volatile agents (e.g. safranal), bitter principles (e.g. picrocrocin) and dye materials (e.g. crocetin and its glycosidic, crocin) (Rio's et al., 1996). Saffron and its constituents are widely evaluated for their pharmacological activities such as treatment of memory impairment, antidepressant, anticonvulsant and especially for their antitumor effect (Abdullaev and Espinosa-Aguirre, 2004).

In animal study, LD50 values of saffron stigma and petal extracts were 1.6 and 6 g/kg (intraperitoneally injection), respectively, in mice. In sub-acute study, the aqueous extract of stigma decreased hematocrit, hemoglobin and erythrocytes but it did not induce any significant pathological effects on different organs such as heart, liver, lung, spleen and kidneys (Karimi et al.,

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2004). Information on toxicology and safety of saffron is not consistent. In some reports doses between 1.2 and 2 g showed nausea and followed vomiting, diarrhea and bleeding (Schmidt et al., 2007). As there is inadequate background information on toxicological evaluation of saffron to give an assurance of safety in developing this spice for foods or pharmaceutical uses, in this study the stigma of saffron was evaluated for short-term safety and tolerability in healthy adult volunteers.

Material and methods

Study design

The study was a double-blind, placebo-controlled study consisting of 1 week treatment. Thirty normal, apparently healthy adults (age range 20–50 years) were selected for the study. Before treatment, pulse rate and blood pressure readings were also taken, and a non-fasting pre-screen blood sample was taken for clinical examination and laboratory (hematology and blood biochemistry) investigations as well as urine analysis and electrocardiogram (ECG). The study outcome measures were also evaluated on the day 8. All participants provided written informed consent prior to the start of the study.

Volunteers

Volunteers were divided into 3 groups of 10 each (5 males and 5 females). Group I received placebo; groups 2 and 3 received 200 and 400 mg saffron tablets, respectively, for 7 days (Tables 1 and 2).

Study centre

This study was done at Vascular Surgery Research Center, Imam Reza Hospital in association with Department of Pharmacology and Toxicology of Mashhad University of Medical Science.

Table 1. Age of the healthy volunteers (years) treated with saffron tablets

	Placebo	Saffron 200 mg	Saffron 400 mg
Female (age, year)	27.40 ± 4.44	25.20 ± 3.34	26.00 ± 3.39
Male (age, year)	30.00 ± 8.00	29.80 ± 9.12	31.40 ± 7.26

Table 2. Weight (kg) of healthy adult volunteers treated with saffron tablets

	Placebo	Saffron 200 mg	Saffron 400 mg
Male (weight, kg)	75.40 ± 2.07	68.40 ± 7.19	72.40 ± 7.33
Female (weight, kg)	57.20 ± 11.36	53.40 ± 7.92	61.00 ± 4.84

Test substance

Plant material

Crocus sativus L. stigma was taken from Novin Saffron Co. Mashhad, IR. Iran. It was formulated as tablets which each tablet contained 200 or 400 mg dried saffron stigma.

Quantification saffron stigma

To quantificate crocin and safranal in an aqueous saffron extraction, a modified method was used (Sujata et al., 1992; Hadizadeh et al., 2007). The extract of authentic stigmata of an aqueous saffron extraction was passed through a 0.2 μm Millipore filter (Millipore, Bedford, MA, USA) and eluted with 100% methanol. These quantification was carried out by Shimadzu HPLC LC-10ADvp system integrated with a Shimadzu SCL-10Avp system controller and a SPD-10Avp UV-visible spectrophotometric on a reversed-phase Shim-pak C18, VP-ODS analytical column (25 cm × 4.6 mm I.D with a 12.0 ± 1.0 nm pore size and 4.6 ± 0.3 μm particle size), using an isocratic mobile phase of acetonitrile:water (76:24%)) at a flow rate of 1.2 ml/min. A Rheodyne Shimadzu Model 7725i injector was used to inject 25 μl of the sample from a 25 μl Hamilton straight-edge needle syringe onto the column. All data were recorded and analyzed on a chromatography workstation Shimadzu Class-VP™ 6.10 software (Hadizadeh et al., 2007). As reported before (Hosseinzadeh et al., 2008), using the calibration curve, the quantification of crocin and safranal in a sample of *C. sativus* extract achieved about 19.7 and 0.25 mg/g, respectively.

Inclusion criteria

Healthy adult volunteers and willing to give voluntary written informed consent were selected to participate in this study. The volunteers were proven to be healthy through clinical examination by the physician along with hematological and biochemical investigations as well as ECG.

Exclusion criteria

Volunteers were excluded from study if any of the following criteria applied at the time of study:

1 – history of allergy to saffron, 2 – history of blood disease, for example: iron deficiently, anemia, hemophilia, 3 – history of cardiovascular disease including vascular or conductive cardiac disease, hypertension, orthostatic hypotension, 4 – history of renal disorder or electrolytes disorder, 5 – history of endocrine disease for example: hypo or hyper-thyroidism, diabetic mellitus, hyperlipidemia, hypercholestrolemia, 6 – history of gynecologic or any menstrual disturbance, 7 – pregnant or lactating women, 8 – addicted to smoking or any substance, 9 – volunteers who have taken any drugs.

Statistical analysis

Data are expressed as mean ± SD. Statistical analysis was done using Student's paired *t*-test with SPSS software. *P*-Values less than 0.05 were considered to be statistically significant.

Results

Through clinical examination showed no gross changes in clinical sign and symptoms in all volunteers after intervention.

No significant differences were noted in the mean values of body weight, sitting systolic and diastolic blood pressure as well as standing diastolic blood pressure. Sitting and standing pulse rate in three groups before and after the intervention was not changed (Table 3). In this study, saffron with higher dose (400 mg) decreased standing systolic blood pressure and mean arterial pressures significantly (Table 3).

ECG recordings discovered no irregularities in all treated volunteers and were within normal limits.

Saffron at a dose of 200 mg decreased RBC, Hb, HCT ($p < 0.05$) and at a dose of 400 mg decreased RBC ($p < 0.05$) but Hb and HCt were decreased near significant (Hb: $p = 0.06$, HCt: $p = 0.09$) (Table 4). Only saffron at a dose of 200 mg decreased platelets, INR and bleeding time (Table 5).

Saffron at a dose of 200 mg increased creatinine ($p < 0.05$) and at a dose of 400 mg increased Na, BUN and creatinine ($p < 0.05$) (Table 6).

Saffron with both doses did not change triglyceride, cholesterol, HDL and LDL parameters after 7-day administration in healthy volunteers (Table 7).

No major adverse events were reported during the trial. Saffron at a dose of 400 mg in 4 volunteers (% 40) increased their mood. One female volunteer in each groups of 200 and 400 mg received saffron showed abnormal uterine bleeding.

Discussion

The result of present study showed that saffron change slightly some clinical and laboratory parameters in the healthy adult volunteers at high oral dosage of 200 and 400 mg of saffron tablets.

In this study, saffron tablet with higher dose (400 mg) decreased to some extent standing systolic blood

Table 3. Effect of *Crocus sativus* stigma tablets on cardiovascular system study done in healthy adult volunteers

Variables	Intervention	Placebo	Saffron 200 mg	Saffron 400 mg
Sitting systolic BP (mmHg)	Before	113.5 ± 13.75	111 ± 9.66	114 ± 9.36
	After	114 ± 6.14	109 ± 11.41	115 ± 4.11
Sitting diastolic BP (mmHg)	Before	67 ± 5.68	63.5 ± 11.06	64.5 ± 6.85
	After	64 ± 5.67	66.5 ± 7.83	66.6 ± 5.05
Standing systolic BP (mmHg)	Before	121.50v10.01	125 ± 8.16	126.5 ± 9.73
	After	123 ± 7.88	120 ± 8.16	115.5 ± 8.31 *
Standing diastolic BP (mmHg)	Before	75.5 ± 8.31	75.5 ± 7.97	75 ± 6.66
	After	72.0 ± 3.49	76.0 ± 6.99	73.0 ± 6.74
Mean sitting arterial pressure (mmHg)	Before	82.49 ± 7.98	79.32 ± 10.25	80.99 ± 7.33
	After	80.66 ± 5.39	80.83 ± 8.47	81.56 ± 4.00
Mean standing arterial pressure (mmHg)	Before	90.83 ± 6.90	91.99 ± 7.10	92.16 ± 7.41
	After	88.99 ± 4.66	90.66 ± 6.04	87.16 ± 7.03 *
Sitting pulse rate (rate/min)	Before	70.5 ± 10.51	70.3 ± 6.86	72.30 ± 6.29
	After	71.6 ± 13.43	68.2 ± 13.43	73.3 ± 7.05
Standing pulse rate (rate/min)	Before	76.7 ± 10.04	78.6 ± 7.41	76.6 ± 4.9
	After	73.7 ± 7.84	77.4 ± 10.24	76.6 ± 7.94

Values presented as the mean ± SEM; $n = 10$ in each group. *$p < 0.05$, as compared to before intervention (paired *t*-test).

Table 4. Effect of *Crocus sativus* stigma tablets on blood counts study done in healthy adult volunteers

Blood cells	Intervention	Placebo group	200 mg group	400 mg group
RBC (million/μl)	Before	5.27±0.66	4.95±0.36	4.87±0.50
	After	5.21±0.78	4.82±0.40*	4.74±0.45*
Hemoglobin (g/dl)	Before	14.54±1.95	14.40±1.52	14.20±1.30
	After	14.19±1.49	14.01±1.27*	13.79±1.27*
Hematocrit (%)	Before	43.35±0.83	44.12±3.78	43.74±3.93
	After	43.60±0.97	42.81±3.56*	42.61±3.77
Mean corpuscular volume (MCV), fl	Before	85.81±7.55	88.88±4.19	89.53±3.10
	After	85.65±7.15	87.93±4.01	89.55±4.46
Mean corpuscular hemoglobin (MCH), pg	Before	27.51±3.04	28.84±2.14	29.01±1.09
	After	28.33±3.49	33.32±14.62	29.13±1.62
Mean corpuscular hemoglobin concentration (MCHC) g/dl	Before	32.23±1.65	32.49±1.14	32.39±0.68
	After	32.56±1.52	32.35±0.88	32.98±1.09
WBC (× 1000/cu mm)	Before	6.16±1.08	6.19±1.65	6.32±1.04
	After	6.47±1.46	6.16±1.60	5.81±1.02
Polymorphonuclear cells (PMN) %	Before	53.39±7.53	55.56±9.85	51.39±7.70
	After	58.60±5.32	57.95±8.93	52.17±9.73
Lymphocyte %	Before	34.60±7.56	36.76±8.95	38.62±6.47
	After	33.97±6.42	36.36±10.88	41.15±7.01

Values presented as the mean±SEM; $n = 10$ in each group. *$p < 0.05$, as compared to before intervention (paired t-test).

Table 5. Effect of *Crocus sativus* stigma tablets on coagulation factors and platelets study done in healthy adult volunteers

Coagulation factors	Intervention	Placebo group	200 mg group	400 mg Group
Platelets (× 1000/cu mm)	Before	251±46.58	232.5±38.31	226.3±69.81
	After	221±58.90	217.7±38.08*	220.9±57.28
Prothrombin time (PT) (sec)	Before	13.42±0.69	13.91±0.93	13.26±0.56
	After	13.02±0.65	13.48±0.83	12.92±0.59
Partial thrombin time (PTT) (sec)	Before	28.89±3.44	27.77±3.40	28.05±3.94
	After	31.29±3.25	28.80±3.65	30.09±4.43
International normalized ratio (INR)	Before	1.07±0.08	1.12±0.06	1.05±0.05
	After	1.08±0.10	1.08±0.09*	1.03±0.06
Bleeding time (sec)	Before	93±17.02	108±32.25	96±23.66
	After	102±20.97	75±32.40*	85±17.79
Clothing time (min)	Before	5.47±0.69	4.74±0.67	5.11±0.71
	After	5.88±0.74	4.62±0.99	5.38±0.89

Values presented as the mean±SEM; $n = 10$ in each group. *$p < 0.05$, as compared to before intervention (paired t-test).

pressure and mean arterial pressures. The aqueous and ethanol extracts of *C. sativus* petals reduced the blood pressure in a dose-dependent manner in rats (Fatehi et al., 2003). Recently, antihypertensive effect of saffron stigma and its constituents safranal and crocin was also seen in rats (unpublished data). A higher antihypertensive effect may be seen in hypertensive patients.

Saffron reduced some hematological parameters but these changes were not dose dependent. Saffron tablet at a dose of 200 mg decreased platelets, INR and bleeding time. However, crocin, as a constituent of saffron, prolonged blood coagulation time in mice, inhibited platelet aggregation in rabbits, prevented thrombus formation in rats and relieved respiratory distress due to pulmonary thrombosis in mice (Ma et al., 1999). A platelet aggregation inhibitor was isolated from stigma of *C. sativus*. The active substance was identified as adenosine (Okano et al., 1992). Thus, this effect needs

Table 6. Effect of *Crocus sativus* stigma tablets on biochemistry function of kidney study done in healthy adult volunteers

Variables	Intervention	Placebo Group	200 mg Group	400 mg Group
Na^+ (mEq/dl)	Before	140.30 ± 2.21	139.60 ± 1.83	138.50 ± 2.27
	After	138.80 ± 3.58	138.10 ± 4.67	140.50 ± 2.79*
K^+ (mEq/dl)	Before	3.89 ± 0.25	4.05 ± 0.29	4.04 ± 0.27
	After	4.07 ± 0.60	4.22 ± 0.37	4.16 ± 0.23
BUN (mg/dl)	Before	13.40 ± 2.21	11.20 ± 3.19	12.30 ± 4.78
	After	14.80 ± 4.77	14.22 ± 0.37	16.00 ± 6.99*
Creatinine (mg/dl)	Before	0.76 ± 0.15	0.73 ± 0.17	0.72 ± 0.20
	After	0.81 ± 0.21	0.91 ± 0.22*	0.89 ± 0.26*

Values presented as the mean ± SEM; $n = 10$ in each group. *$p < 0.05$, as compared to before intervention (paired t-test).

Table 7. Effect of *Crocus sativus* stigma tablets on lipid profiles study done in healthy adult volunteers

Lipid profiles	Intervention	Placebo group	200 mg group	400 mg group
Triglyceride (mg/dl)	Before	125.60 ± 94.05	125.90 ± 105.07	137.30 ± 81.49
	After	133.90 ± 76.77	111.40 ± 69.87	125.70 ± 94.88
Cholesterol (mg/dl)	Before	177.90 ± 35.39	167.50 ± 34.89	192.80 ± 57.23
	After	187.30 ± 40.22	158.50 ± 31.60	196.90 ± 41.24
HDL (mg/dl)	Before	48.8 ± 4.15	54.50 ± 15.83	49.20 ± 7.82
	After	50.4 ± 7.15	47.60 ± 8.36	47.40 ± 11.93
LDL (mg/dl)	Before	103.00 ± 33.19	96.60 ± 23.09	119.40 ± 48.44
	After	108.50 ± 29.40	91.50 ± 29.01	124.30 ± 29.15

Values presented as the mean ± SEM; $n = 10$ in each group. *$p < 0.05$, as compared to before intervention (paired t-test).

further study in a larger sample size and longer time period.

Saffron increased some kidney function parameters such as creatinine and BUN. However, this effect is not important clinically and these factors are in normal range.

Saffron with both doses did not change triglyceride, cholesterol, HDL and LDL parameters after 7-day administration in healthy volunteers. In rabbits, after 8 weeks of feeding on high lipid diet and supplementation with crocetin, a constituent of saffron stigma, markedly reduced the progression of atherosclerotic lesions and plasma levels of oxidized low-density lipoprotein (Ox-LDL), whereas plasma lipids level remained unchanged. These findings suggest that suppression of LDL oxidation by crocetin contributes, at least partly, to the attenuation of atherosclerosis (Zheng et al., 2006). However, in another study in quail and at the 9th week, the atherosclerosis model was established by feeding hyperlipidamic diet. Crocetin reduced the levels of serum total cholesterol, triglyceride, low density lipoprotein cholesterol and inhibit the formation of aortic plaque (He et al., 2007).

In experimental hyperlipemia rats with 2 months feeding heavy cholesterol, crocin decreased to a great extent the content of cholesterol, triglyceride and density lipoprotein in blood and also increased the content of high density lipoprotein (Xu et al., 2005). Although in our study saffron tablets did not change lipid profile but it seems in a longer period study (at least 2 months) saffron may reduce serum lipids in especially hyperlipidemic patients.

No major adverse events were reported during the trial. Saffron at a dose of 400 mg in 4 volunteers (% 40) increased their mood. Our previous studies showed that saffron and its constituents have antidepressant activity in mice (Karimi et al., 2001; Hosseinzadeh et al., 2004). Recently, the antidepressant activity of saffron stigma and petal has been evaluated in clinical trials (Akhondzadeh et al., 2005; Akhondzadeh et al., 2007).

One female volunteer in each groups of 200 and 400 mg administration of saffron showed abnormal uterine bleeding. Saffron induced uterine stimulant and estrogenic effects in guinea pigs and mice, respectively (Chang et al., 1964). Saffron induces menstruation (an emmenagogue) and in traditional medicine, the aqueous extract of saffron has been used for amenorrhea and dysmenorrhea.

In respect to dose of saffron, in the previous studies different amounts of this plant were administered. In a double-blind, placebo-controlled, single-centre and randomized trial, depressed patients received a capsule of saffron 30 mg/day (an ethanol extract, about 60 mg dried powder) for a 6-week study (Akhondzadeh et al., 2005). In a recent study, women were randomly assigned to receive the same dose for the treatment of premenstrual syndrome during two menstrual cycles (about 2 months) (Agha-Hosseini et al., 2008). In antioxidant study in human subjects, 50 mg of saffron dissolved in 100 ml of milk was administered twice a day for 6 weeks (Verma and Bordia, 1998). For estimation of maximum tolerated dose, we studied higher doses of saffron 200 and 400 mg (about 4–6 times of the previous doses) for 1 week. Our results are encouraging, although the short study time (1 week) and small sample size (20 subjects) limit assurance in the results.

This study showed that saffron tablets may change some hematological and biochemical parameters. However, these alterations were in normal ranges and they were not important clinically.

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