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A Prospective Double-blind Randomized Placebo-controlled Study of the Effect of Saffron (*Crocus sativus* Linn.) on Semen Parameters and Seminal Plasma Antioxidant Capacity in Infertile Men with Idiopathic Oligoasthenoteratozoospermia

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Male factor infertility is a multifactorial disorder that affects a significant percentage of infertile couples; however, many of them remained untreated. In recent years, considerable numbers of infertile men have sought 'herbal remedies' as an effective treatment. Among 'herbal remedies', saffron is recommended for male infertility in our community. The effect of saffron was evaluated compared with placebo for the treatment of idiopathic male factor infertility. The study included 260 infertile men with idiopathic oligoasthenoteratozoospermia (OAT) who were randomized to saffron 60 mg/day (130, group 1) or a similar regimen of placebo (130, group 2) for 26 weeks. The two groups were compared for changes in semen parameters and total seminal plasma antioxidant capacity. Saffron administration did not result in beneficial effects. At the end of the study no statistically significant improvements were observed in either group in any of the studied semen parameters (sperm density, morphology and motility) (all $p = 0.1$). At the end of the trial, patients in group 1 had a mean motility of 25.7 ± 2.4%, which was not statistically different from the mean of 24.9 ± 2.8% in the placebo group ($p = 0.1$). Normal sperm morphology was 18.7 ± 4.7% and 18.4 ± 4.3%, in groups 1 and 2, respectively ($p = 0.1$). Patients treated with saffron and placebo had a mean sperm density of 20.5 ± 4.6% and 21.4 ± 4.6% per mL, respectively ($p = 0.1$). Saffron administration did not improve total seminal plasma antioxidant capacity, compared with baseline ($p = 0.1$) and placebo subjects ($p = 0.1$). Based on Pearson correlations, each semen parameter did not correlate significantly with treatment duration, including sperm density ($r = 0.146$, $p = 0.13$), percent of motile sperm ($r = 0.145$, $p = 0.15$) and percent of sperm with normal morphology ($r = 0.125$, $p = 0.30$). Saffron does not statistically significantly improve semen parameters in infertile men with idiopathic OAT. If medical professionals want to prescribe herbal remedies for male infertility, previous rigorous scientific investigations, documenting their safety and efficacy are required.

Keywords: infertility; treatment; male factor; saffron; *Crocus sativus*.

INTRODUCTION

Infertility occurs in about 15% of couples (de Kretser, 1997; Safarinejad, 2008) and a male factor is implicated in up to half of these cases (Brugh and Lipshultz, 2004). In a significant number of cases of male infertility the etiology and pathogenesis are still not fully understood and are referred to as idiopathic infertility (Deng *et al.*, 2008). Several reports indicate that, over the past few decades, the overall quality of semen has declined considerably worldwide (Auger *et al.*, 1995; Carlsen *et al.*, 1992). This decline has been associated with industrialization. This denotes that environmental factors, the use of chemicals and repeated exposure to hazardous compounds likely affect the quality of semen (Maureen, 1997). Despite major advances in genetics, diagnosis and treatment of infertility, a significant number of couples with male factor infertility still remain untreated. The social and psychological consequences of infertility are devastating, especially in developing countries. The usual scenario is extramarital affairs, divorce or polygamy (Dyer *et al.*, 2002). Naturally, significant numbers of infertile couples in developing countries seek solutions from nutritional supplementation and herbal remedies (Barden-O'Fallon, 2005). Herbal medicines are products derived from naturally occurring plants with medical properties (Physicians' Desk Reference, 2004). Nutritional supplements and herbal medicines have been used for centuries. The use of herbal remedies is becoming more and more common in the Western world too. One study reported an increase of 380% in the use of herbal remedies and nutritional supplements in the United States during a 10-year period in the 1990s (Eisenberg *et al.*,

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1998). It has been shown that nutritional supplementations such as selenium, *N*-acetyl-cysteine (Safarinejad and Safarinejad, 2009), omega-3 (Safarinejad *et al*., 2010a) and co-enzyme Q10 (Safarinejad, 2009) have improved semen parameters. Administration of herbal remedies for the treatment of infertility has recently become popular, despite a lack of scientific studies to assess their effectiveness and safety (Agarwal and Said, 2003). In traditional medicine, saffron is also suggested as an aphrodisiac herbal remedy (Madan *et al*., 1966). The aphrodisiac properties of *Crocus sativus* stigma aqueous extract and its constituent crocin have been shown in previous studies (Safarinejad *et al*., 2010b; Hosseinzadeh *et al*., 2008; Shamsa *et al*., 2009). Saffron spice, the most expensive spice in the world, comes from the dried stigmas of *Crocus sativus* Linn. and nowadays its main use is as a foodstuff (Maggi *et al*., 2009). It is cultivated in various places worldwide, but 90% of 190 ton annual production of saffron, is produced in Iran (Fernandez, 2004; Negbi, 1999). Saffron is recommended as a treatment of male factor infertility in our community. People can obtain easily this spice from grocers. The main active ingredients in saffron are: glucosyl esters of crocetin (8,8′-diapocarotene-8,8′-dioic acid; $C_{20}H_{24}O_4$), water-soluble glycosidic *cis*- and *trans*-carotenoids crocins, both accountable for its colouring property, picrocrocin ($C_{16}H_{26}O_7$) for the bitter taste and safranal ($C_{10}H_{14}O$) for the aroma (Carmona *et al*., 2006; Lozano *et al*., 1999).

In the past decade, interest in the influence of saffron carotenoids on human health is increasing. Saffron and its constituents such as safranal and crocin have antioxidant properties (Assimopoulou *et al*., 2005). These carotenoids scavenge free radicals, especially superoxide anions (Erben-Russ *et al*., 1987) and thus protect cells from oxidative damage. The deleterious effects of reactive oxygen species (ROS) on spermatozoa were shown more than 60 years ago (Iwasaki and Gagnon, 1992). There are several reports that the ROS produced by leukocytes and/or by spermatozoa have detrimental effects on sperm function (Aitkin *et al*., 1994). Like most cells, spermatozoa are equipped with antioxidant enzymes such as superoxide dismutase, glutathione peroxidase and catalase to detoxify harmful excessive ROS and to prevent cell damage. An imbalance (oxidative stress) between ROS production and total antioxidant capacity in seminal fluid is correlated with male infertility (Sharma *et al*., 1999). Because of its powerful antioxidant activity, saffron extract, crocetin or crocin could be useful in the therapy of idiopathic male factor infertility.

Despite a widespread belief in the worthiness of saffron to treat male infertility, there have been no published, randomized placebo-controlled prospective trials adequately to address this issue. The current study tested the belief that saffron is an effective remedy to treat male factor infertility.

MATERIALS AND METHODS

Subjects. From July 2008 to August 2009, 284 men with primary infertility who did not achieve a pregnancy after at least 2 years of unprotected intercourse with the same partner were screened for eligibility. Couples who had been trying to conceive for more than 2 years were enrolled in this study. The ages of the men ranged from 24 to 41 years (28.6 ± 5.4), with 4.1 ± 2.4 years of infertility.

Male infertility was diagnosed if one or more standard semen parameters were below the cutoff levels accepted by World Health Organization (WHO) (1999). The criteria for normal semen parameters were sperm density less than 20×10^6/mL, sperm motility less than 50%, normal morphology less than 30% and/or semen volume less than 2 mL. All study subjects had idiopathic oligoasthenoteratozoospermia (OAT). There was no apparent pathology influencing their fertility status. All of the men were naïve to treatment. Fertile female partners had been diagnosed via extensive infertility evaluation, including physical examination, baseline body temperature, luteal phase progesterone, normal haematological and biochemical values, serum assay for sexual and thyroid hormones; antiphospholipid and anticardiolipin antibodies; lupus anticoagulant; absence of sperm-immobilizing antibodies in their sera, and hysterosalpingography. Cervical cultures for Ureaplasma, Mycoplasma, Chlamydia and bacterial vaginosis were also carried out as needed. Female partners with abnormal findings on hysterosalpingography underwent laparoscopy and/or hysteroscopy.

After explanation of the trial requirements to participants, all of them gave informed consent. The investigation was conducted in accordance with the International Conference on Harmonisation-Good Clinical Practice (ICH-GCP) guidelines and the principles of the Declaration of Helsinki.

Inclusion/exclusion criteria. Patients were included in the study if they were diagnosed with a primary male factor infertility, were younger than 45 years, had been unable to conceive a child for > 24 months before the study with the same partner, had a total testicular volume > 12 mL, and had a normal fertile female partner. No participants were on medications known to affect spermatogenesis.

Patients with abnormal testes on physical examination; azoospermia or severe oligozoospermia (sperm count less than 5 million per mL); a history of epididymo-orchitis, prostatitis, genital trauma, testicular torsion, inguinoscrotal surgery, cryptorchidism, or varicocele; use of cytotoxic drugs, immunosuppressants, androgens or antiandrogens; drug, alcohol or substance abuse; hepatobiliary disease; significant renal insufficiency; any endocrinopathy including hypogonadism, and thyroid disease, were excluded from the study. Patients were also excluded from participation if they had Y chromosome microdeletions or karyotype abnormalities; occupational and environmental exposures to potential reproductive toxins; a body mass index (BMI) of 30 kg/m^2 or greater; and severe general, neurological or psychological diseases.

Evaluations. All patients were evaluated with a complete medical and reproductive history, detailed physical examination and semen analyses. The endocrinological evaluation included assays of luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL), thyroid stimulating hormone (TSH) and testosterone. Karyotype analysis and Y chromosome micro-deletion evaluation were completed in all

the men. The presence of varicocele was determined by colour Doppler ultrasound during the Valsalva manoeuvre. At baseline, a minimum of three semen samples was analysed, separated by a 4-week interval.

Plant material. The dried saffron (*Crocus sativus* L.) stigma was purchased from Novin Zaferan Co. Mashhad, Iran.

The stigma extract was prepared using the procedure as described by Akhondzadeh *et al.* (2005). In brief, 120 g of dried and milled petal of *Crocus sativus* L. was extracted with 1800 mL ethanol (80%) in three steps, using the percolation method. Then the production of ethanol extract was dried at a temperature of 35–40°C by the evaporation procedure. The final production was formulated as a capsule. The active ingredients of each capsule were *Crocus sativus* (15 mg), sodium starch glycolate as disintegrant, lactose as filler and magnesium stearate as lubricant.

Randomization and treatment protocol. A 26-week, randomized, placebo-controlled double-blind study was performed to compare the effects of saffron against placebo. Eligible participants were randomly allocated to one of two groups.

Group 1 (n = 130) received saffron as two capsules twice daily (total daily saffron dosage of 60 mg). Group 2 (n = 130) received two identical placebo capsules twice daily which contained starch. The capsules containing saffron or placebo were identical and had been conditioned in numbered boxes according to randomized numbers. All patients and study personnel were unaware of group treatment assignment.

Patients were asked to follow their usual diet to avoid effects due to variable antioxidant intake in food. Patients were visited every 4 weeks during the treatment period. At each follow up visit two semen analyses were performed within a 2-week period. Mean pretreatment semen parameters were compared with mean posttreatment parameters at follow up visits. Compliance was assessed by asking patients about missed doses and assessment of capsule counts when bottles of study medication were collected.

Semen analysis. Semen samples were obtained after 3 days abstinence. Samples were collected into sterile containers and allowed to liquefy at 37°C for 30 min. A routine semen analysis was carried out for sperm concentration, percentage motility and morphology according to WHO criteria (WHO, 1999). Each sample was tested at least twice for sperm density, motility and morphology. The total number of sperm in the ejaculate was calculated as the sperm concentration times specimen volume.

Genetic analyses. Karyotyping was carried out with GTG banding using the peripheral blood lymphocyte technique. Y chromosome microdeletion, including AZFa, AZFb and AZFc regions was performed using polymerase chain reaction amplification.

Seminal plasma antioxidant status. Superoxide dismutase (SOD)-like activity was measured by the reduction of nitro-blue tetrazolium (NBT) by the xanthine-xanthine oxidase system as described by Zini *et al.* (Zini *et al.*, 2002; Safarinejad, 2010). Seminal plasma enzyme activity leading to 50% reduction of NBT was accepted as one unit of SOD-like activity. Catalase-like activity was measured as the removal of exogenous hydrogen peroxide (H_2O_2) using the method described by Yeung *et al.* (Safarinejad, 2010; Yeung *et al.*, 1996). The quantity of seminal plasma capable of decreasing the amount of hydrogen peroxide present in solution by 50% was defined as one unit of catalase-like activity (Safarinejad, 2010).

Safety assessment. At each follow up visit the safety profile was assessed by monitoring of adverse events and measurement of vital signs as well as by serum chemistry, haematology, and urinalysis. Treatment-emergent adverse events (TEAEs), defined as adverse events first appearing or worsening during treatment. Subjects reported any adverse events that occurred during the study. The severity and relation to study drug of TEAEs were summarized by the Medical Dictionary for Regulatory Activities (MedDRA version 7.0) for severity and relationship to study drug.

Statistical analysis. Sample size was powered for a difference of approximately 1 SD between the saffron and placebo group. Given these assumptions, and with an α risk of 5% (2-tailed) and a β risk of 20%, it was calculated that 110 subjects per arm were required to achieve sufficient power to allow comparison of both treatments. Taking into account 15% dropout rates, 40 additional patients were included to guarantee sufficient power, resulting in 130 subjects per arm and 284 participants in total.

Results are expressed as mean plus or minus standard deviation of the mean. Continuous and categorical data were analysed for significance between the groups using one-way analysis of variance and chi-square tests, respectively. Student's t-test was used to determine significant differences between groups with variables normally distributed; when not, a non-parametric Mann–Whitney U-test was carried-out. Pearson's coefficient was used to evaluate correlations. Values of $p < 0.05$ were considered significant. Statistical analysis of the data was performed with the Statistical Package for Social Sciences (version 16.0 for Windows; SPSS, Inc., Chicago, IL).

RESULTS

Subject outcomes

Two hundred sixty subjects were randomized at baseline to receive saffron (60 mg/day) (n = 130) or placebo (n = 130). There were no significant differences in any baseline demographic and clinical characteristics among the study groups (Table 1). One hundred fourteen subjects (87.7%) in the saffron group, and 116 subjects (89.2%) in the placebo group completed the 26-week study period. Thirty subjects withdrew from the study prematurely after randomization. Reasons for discontinuation were withdrawal of consent (nine subjects), adverse events (AEs) (five subjects), lost to follow-up (eight subjects) and protocol violation (eight subjects) (Fig 1). Of the five subjects who withdrew due to AEs, one was on placebo (headache), and four were on saffron (nausea, hypoma-

Table 1. Baseline demographics, serum hormones and semen parameters of study groups

Characteristic	Saffron (n = 130)	Placebo (n = 130)	p value
Age (year)	28.4 ± 5.2	28.8 ± 5.6	NS
Infertility duration (year)	4.4 ± 2.2	4.6 ± 2.6	NS
BMI (kg/m^2)	26.8 ± 2.6	26.6 ± 2.4	NS
Occupational status No. (%)			
Employed	115 (88.5)	116 (89.2)	NS
Unemployed	15 (11.5)	14 (10.8)	NS
Serum hormones			
Testosterone (nmol/L)	15.4 ± 4.8	15.6 ± 4.6	NS
LH (IU/L)	12.2 ± 2.4	12.4 ± 2.2	NS
FSH (IU/L)	16.8 ± 4.2	16.4 ± 4.6	NS
PRL (pmol/L)	363 ± 117	367 ± 122	NS
TSH (mIU/mL)	1.7 ± 0.7	1.7 ± 0.7	NS
Semen parameters			
Ejaculate volume (mL)	2.7 ± 1.4	2.8 ± 1.3	NS
Total sperm/ejaculate (× 10^6)	47.8 ± 12.4	47.8 ± 12.2	NS
Sperm density (× 10^6/mL)	21.2 ± 4.4	20.9 ± 4.6	NS
Motility (% motile)	24.3 ± 2.4	23.8 ± 2.6	NS
Morphology (% normal)	17.2 ± 4.6	17.3 ± 4.7	NS
Haematological parameter:			
Haemoglobin (mg/dL)	14.4 ± 0.36	14.3 ± 0.38	NS
White blood cells (10^3)	7.68 ± 2.12	7.72 ± 2.16	NS
Red blood cells (10^9)	8.28 ± 0.54	8.24 ± 0.54	NS
Platelets (10^3)	872 ± 123	878 ± 122	NS
Seminal plasma antioxidants			
SOD-like activity (U/mL)	311 ± 14	314 ± 16	NS
Catalase-like activity (U/mL)	36.6 ± 1.4	37.1 ± 1.6	NS

LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; PRL, prolactin; BMI, body mass index; SOD, superoxide dismutase; NS, not significant.

nia, increased appetite and headache, one each). The study groups appeared well matched in terms of baseline demographic characteristics, including age.

Serum hormones

Mean baseline serum hormone concentrations were not significantly different among groups at baseline (Table 1). There were no significant changes from baseline or among treatment groups in serum hormones (Table 2) (all $p = 0.1$).

Testicular volume

As measured by ultrasonography, the mean testicular volume was 23.6 ± 2.7 and 23.4 ± 2.9 mL in the saffron and placebo groups, respectively. There was no significant difference in testis volume between the two groups ($p = 0.1$).

Semen parameters

Mean total semen volume, sperm count, sperm concentration, sperm motility and sperm morphology did not significantly differ between treatment groups at baseline (Table 1). The mean total sperm counts in saffron patients and placebo subjects were 46.4 ± 12.2 million and 47.4 ± 12.2 million, respectively ($p = 0.1$). Saffron patients had a mean sperm motility of 25.7 ± 2.4%, which was not significantly different from the mean for placebo group (24.9 ± 2.8%, $p = 0.1$).

The mean normal sperm forms per ejaculate for group 1 and group 2 was 18.7 ± 4.7%, and 18.4 ± 4.3%, respectively ($p = 0.1$). There was no significant difference in the morphology of sperm from saffron patients and placebo subjects. The mean sperm count, sperm concentration, sperm motility and sperm morphology remained relatively constant in each of the treatment groups throughout the study period (all $p = 0.1$). These semen parameters were close to those obtained at baseline. In other words, sperm density, motility and morphology remained unchanged throughout the study period (Table 2) (Figs 2–4). According to analysis of variance with multiple comparisons, treatment with saffron did not cause an increase in seminal plasma SOD-like and catalase-like activity ($p = 0.1$) (Table 2). No correlation was found between treatment duration with saffron and sperm count ($r = 0.146$, $p = 0.13$) as well as mean sperm motility ($r = 0.145$, $p = 0.15$) and sperm morphology ($r = 0.125$, $p = 0.30$).

Table 2. Summary of semen parameters, reproductive hormones, haematological parameters and antioxidant status of seminal plasma at the end of 26-week treatment period with *Crocus sativus*

Variable	Saffron (n = 130)	Placebo (n = 130)	p value
Serum hormones			
Testosterone (nmol/L)	15.6 ± 4.4	15.8 ± 4.2	NS
LH (IU/L)	12.4 ± 2.2	12.6 ± 2.4	NS
FSH (IU/L)	16.2 ± 4.4	16.8 ± 4.2	NS
PRL (pmol/L)	371 ± 112	377 ± 120	NS
TSH (mIU/mL)	1.7 ± 0.8	1.7 ± 0.7	NS
Semen parameters			
Ejaculate volume (mL)	2.6 ± 1.4	2.7 ± 1.4	NS
Total sperm/ejaculate (× 10^6)	46.4 ± 12.2	47.4 ± 12.2	NS
Sperm density (× 10^6/mL)	20.5 ± 4.6	21.4 ± 4.6	NS
Motility (% motile)	25.7 ± 2.4	24.9 ± 2.8	NS
Morphology (% normal)	18.7 ± 4.7	18.4 ± 4.3	NS
Haematological parameter:			
Haemoglobin (mg/dL)	12.2 ± 0.32	14.5 ± 0.36	0.03
White blood cells (10^3)	6.28 ± 2.14	7.78 ± 2.14	0.01
Red blood cells (10^9)	6.68 ± 0.56	8.28 ± 0.52	0.01
Platelets (10^3)	752 ± 118	867 ± 127	0.01
Seminal plasma antioxidants			
SOD-like activity (U/mL)	313 ± 16	310 ± 12	NS
Catalase-like activity (U/mL)	37.7 ± 1.6	37.6 ± 1.6	NS

LH, luteinizing hormone; FSH, follicle stimulating hormone; TSH, thyroid stimulating hormone; PRL, prolactin; SOD, superoxide dismutase; NS, not significant.

Adverse events

The adverse events profiles of the two medications are shown in Table 3. Most adverse events were mild to moderate in nature. Four patients in the saffron group permanently discontinued because of adverse events.

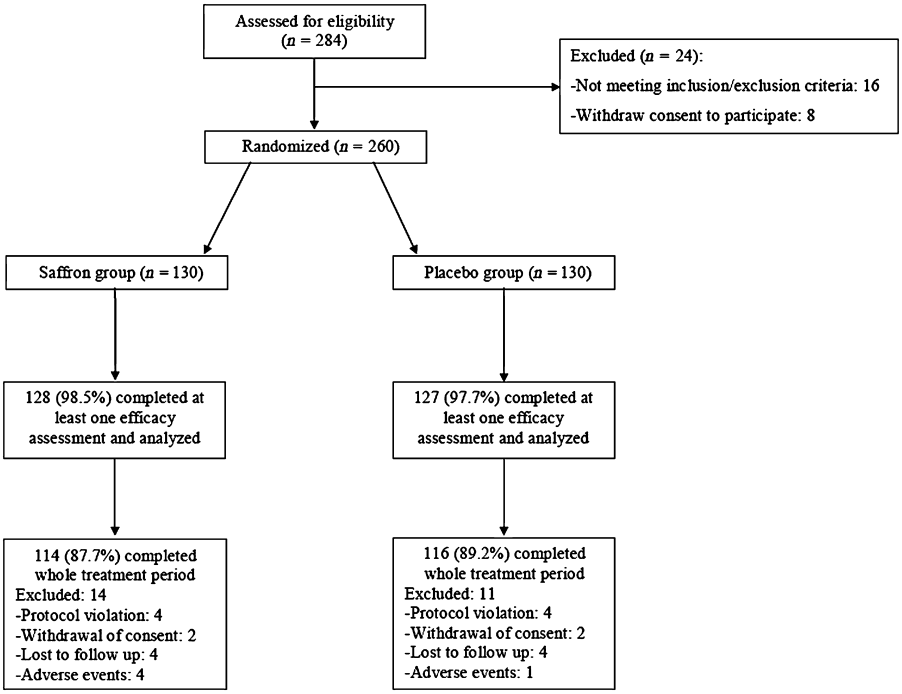

Figure 1. The participant flow diagram.

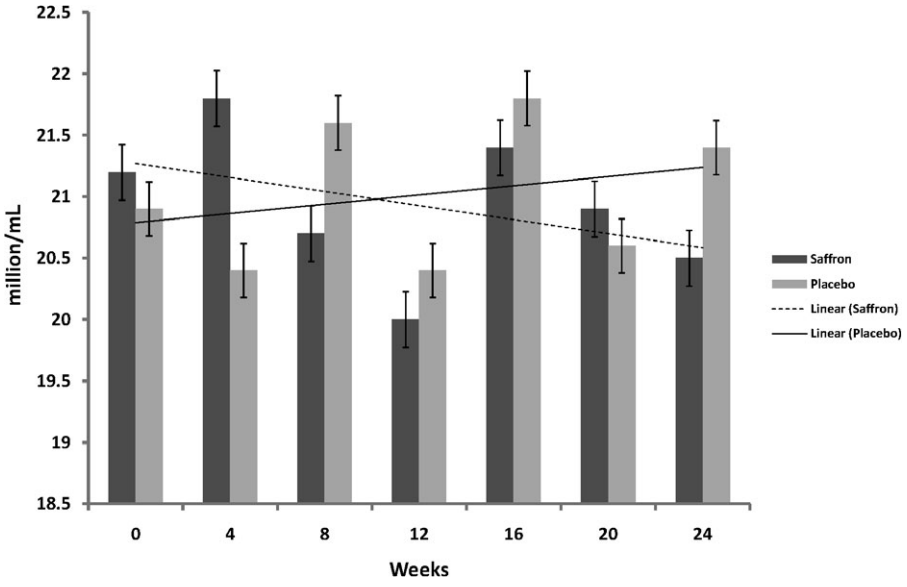

Figure 2. Effect of *Crocus sativus* on sperm density in different follow-up time points during 26-week study period.

The adverse events that resulted in discontinuation were severe headache in one patient, nausea in two, hypomania in one and increased appetite in one. All these AEs were regarded as mild except for the one nausea, which was listed as moderate. There were no serious adverse events with either medication. However, clinically significant effects on laboratory parameters and vital signs were noted in patients while taking saffron. The mean blood pressure (BP) at baseline in the saffron and placebo groups was 127/74 ± 8/6 mmHg and 126/72 ± 8/6 mmHg, respectively. During treatment with saffron and placebo, the mean BP was 112/66 ± 7/6 mmHg for saffron patients and 124/72 ± 8/6 mmHg for placebo patients, representing a mean BP decrease of 15.8 mmHg (–11.8% mean systolic BP and –10.8% mean diastolic BP). The difference in mean BP between treatment groups was significant for systolic and diastolic blood pressures (p = 0.02). Serial haematologic laboratory tests, showed decreases in peripheral blood leukocytes, red blood cells and platelets with saffron supplementation. The mean baseline white blood cell count (7.68 ± 2.12 × 10^3/mL) decreased by 18.2% (6.28 ± 2.14 × 10^3/mL) in the saffron group at the end of the trial (p = 0.0001). A significant decrease was also noted in the red blood cell count (decreased by 19.2%, p = 0.0001) and platelet count (decreased by 13.8%, p = 0.0001) in patients while taking saffron. These decreases started after 8 weeks of treatment, and became progressively more prominent with continued use of saffron (Figs 5–8).

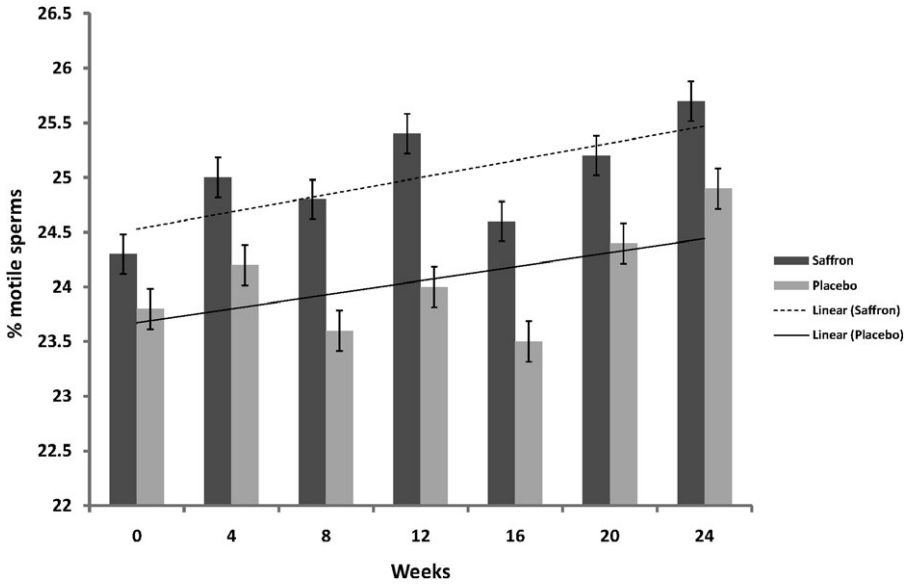

Figure 3. Effect of *Crocus sativus* on percent motile sperms in different follow-up points during 26-week study period.

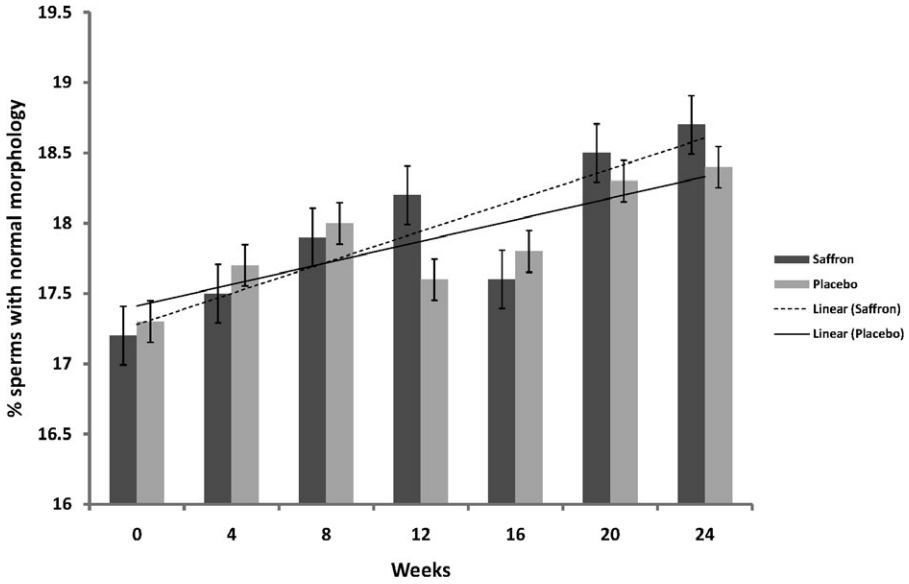

Figure 4. Effect of *Crocus sativus* on percent sperms with normal morphology in different follow-up points during 26-week study period.

Table 3. Treatment-emergent adverse events listed by decreasing frequency overall

Adverse event *n* (%)	Saffron	Placebo	*p* value
Decreased platelet count (> 100^3/mL)	81 (62.3)	0	0.0001
Decreased leukocyte count (> 1000/mL)	78 (60.0)	0	0.0001
Decreased red blood cell count (> 1000/mL)	72 (55.4)	0	0.0001
Decreased appetite	17 (13.1)	1 (0.77)	0.001
Increased appetite	17 (13.1)	1 (0.77)	0.001
Headache	15 (11.5)	4 (3.1)	0.01
Nausea	12 (9.2)	2 (1.5)	0.01
Sedation	10 (7.7)	0	0.001
Hypomania	10 (7.7)	0	0.001

DISCUSSION

To our knowledge this double-blind, placebo-controlled randomized study represents the first evaluation to date comparing saffron and placebo for male infertility. The results of our study allow definitive conclusions to be drawn on the effects of saffron in relation to semen parameters. The results of the present study show that saffron is not effective in improving the semen parameters in men with idiopathic OAT. Oxidative stress has been reported to be a major cause of male factor infertility. Indeed, a large proportion of infertile men have increased levels of seminal ROS (Sharma *et al*., 1999; Pasqualotto *et al*., 2000). Saffron has been proposed as an 'herbal remedy' for male infertility. Its main active compounds are carotenoids that might scavenge seminal plasma free radicals by increasing the seminal

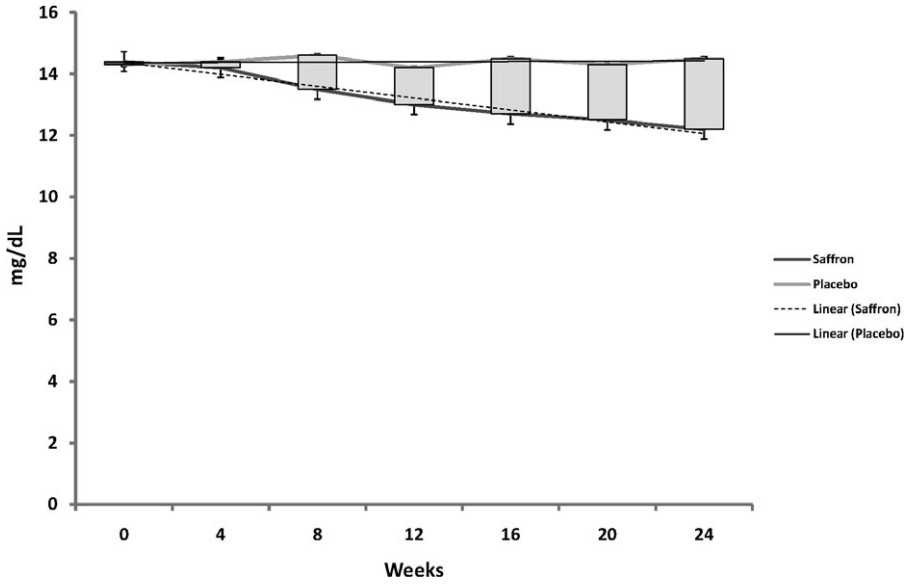

Figure 5. Effect of *Crocus sativus* on blood haemoglobin in different follow-up points during 26-week study period.

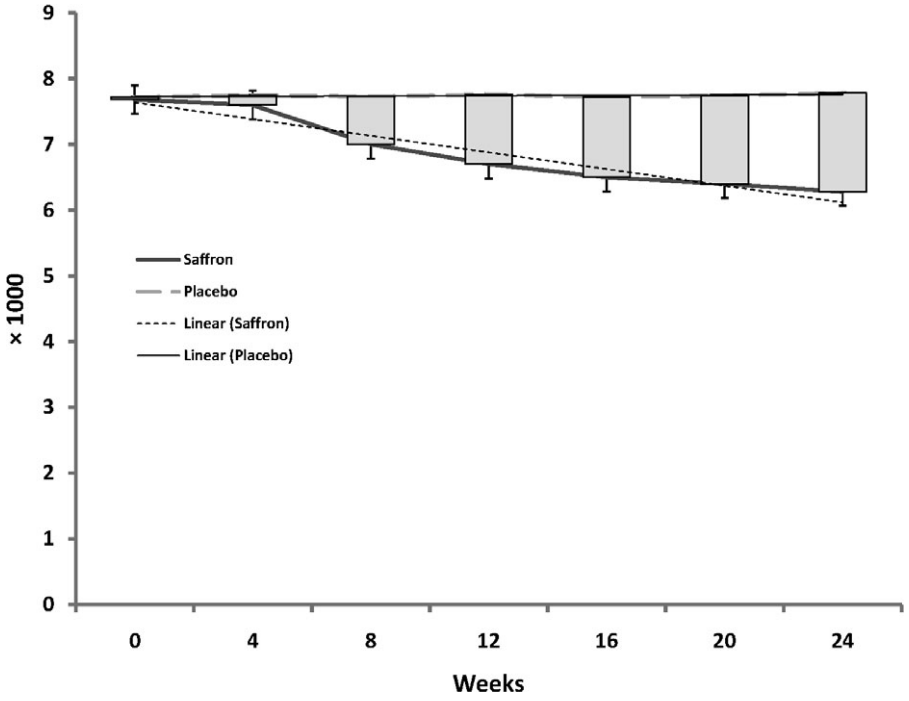

Figure 6. Effect of *Crocus sativus* on white blood cells count in different follow-up points during 26-week study period.

plasma total antioxidant capacity. It has been shown that, to be effective as a ROS scavenger, a candidate medication would have to increase seminal plasma total antioxidant capacity. As evident from the results of this study, saffron supplementation did not result in increased levels of seminal plasma SOD-like and catalase-like activities. We could find no similar studies for comparison in the literature.

Nutritional supplements and herbal remedies are an expanding business, especially via the Internet. Often there are no established regulations regarding their production, and consumers tend to have an unmotivated confidence in 'natural medicines' falsely believing them safe and free from side-effects (Venhuis *et al*., 2008). In this study saffron administration significantly decreased peripheral blood leukocytes, red blood cells and platelets. Although these decreases were not clinically significant, but might be potentially dangerous in long term saffron usage or with the administration of higher doses of saffron. In a study by Modaghegh *et al*. (2008), 10 subjects received 400 mg saffron daily for 7 days. The authors concluded that, despite changes in some haematological parameters, these alterations were in normal ranges and they were not clinically important. We believe that 400 mg saffron per day is a very high dosage, and 7 day administration is not enough time to affect bone marrow haematopoiesis. Indeed, even after administration of immunosuppressant drugs, peripheral blood cells, will not be affected within 7 days. Therefore, conclusions in the above cited study might be interpreted with

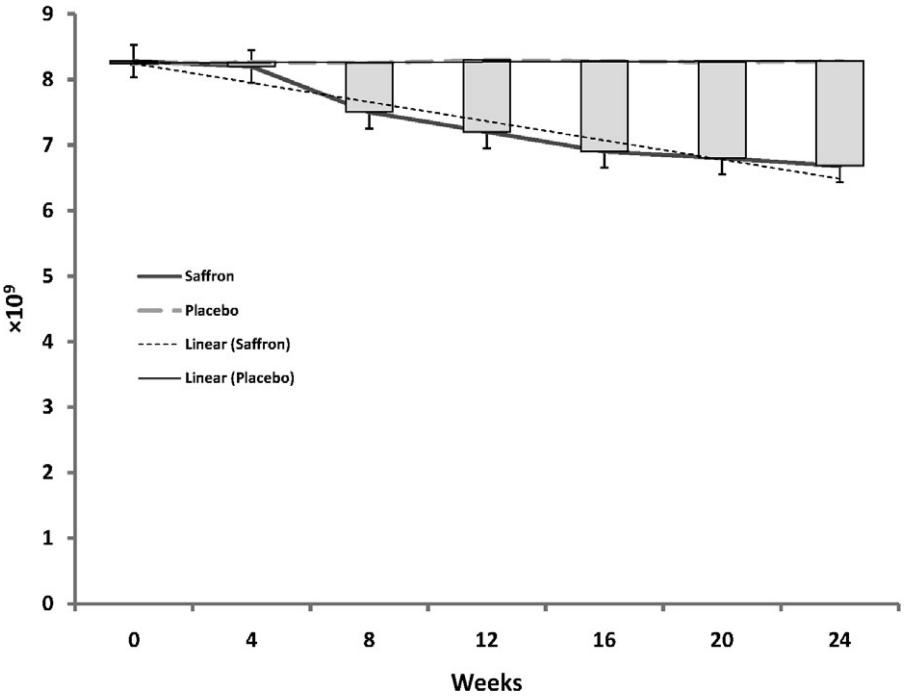

Figure 7. Effect of *Crocus sativus* on red blood cell count in different follow-up points during 26-week study period.

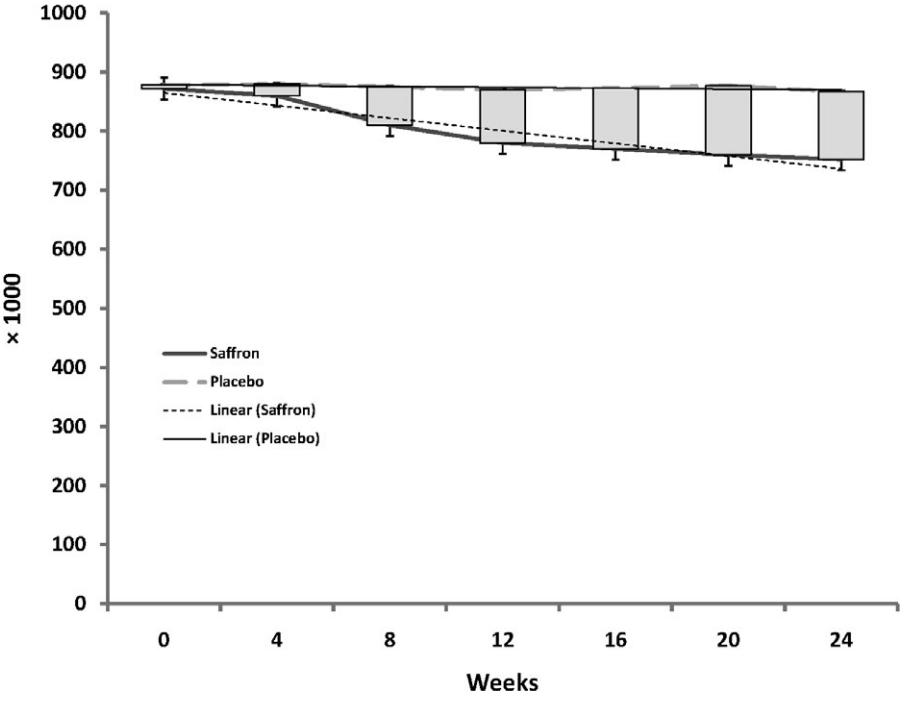

Figure 8. Effect of *Crocus sativus* on platelets count in different follow-up points during 26-week study period.

caution. In subjects taking the saffron, serious haematological side effects can take place over a period of time. We do not recommend higher doses of saffron for a long period. Public interest in the use of saffron for the treatment of male infertility is likely to increase. In Iran, herbal remedies are very available alternative therapies, and many people use herbs to treat their diseases. In our community herbal remedies usually are recommended and prescribed by grocers. Typically they do not have any scientific medical knowledge.

Global demands for herbal products that treat various diseases are increasing (Cherdshewasart *et al.*, 2008). The results of this study provide evidence to support the scientific investigations about the safety and efficacy of recommended herbal products.

The advantages of this trial are the appropriate study power and adequate duration of treatment. A complete spermatogenesis cycle needs to 72 days to take place. In this study, saffron was administered for 24 weeks (about two spermatogenesis cycles). Therefore there was

enough time to encounter potential beneficial effects from saffron supplementation.

CONCLUSION

The present findings do not provide evidence that the saffron administration improves semen values.

Natural health remedies claiming efficacy for male infertility, should be considered with caution, especially when marketed without sound scientific medical background. Men with infertility should consult physicians for safe management.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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