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The effect of saffron, *Crocus sativus* stigma, extract and its constituents, safranal and crocin on sexual behaviors in normal male rats

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Abstract

In this study, the aphrodisiac activities of *Crocus sativus* stigma aqueous extract and its constituents, safranal and crocin, were evaluated in male rats. The aqueous extract (80, 160 and 320 mg/kg body wt.), crocin (100, 200 and 400 mg/kg body wt.), safranal (0.1, 0.2 and 0.4 ml/kg), sildenafil (60 mg/kg body wt., as a positive control) and saline were administered intraperitoneally to male rats. Mounting frequency (MF), intromission frequency (IF), erection frequency (EF), mount latency (ML), intromission latency (IL) and ejaculation latency (EL) were the factors evaluated during the sexual behavior study. Crocin, at all doses, and the extract, especially at doses 160 and 320 mg/kg body wt., increased MF, IF and EF behaviors and reduced EL, IL and ML parameters. Safranal did not show aphrodisiac effects. The present study reveals an aphrodisiac activity of saffron aqueous extract and its constituent crocin.

Keywords: Saffron; *Crocus sativus*; Crocin; Safranal; Sildenafil; Aphrodisiac activity; Sexual activity

Introduction

Sexual dysfunction is a serious medical and social symptom that occurs in 10–52% of men and 25–63% of women. Of men aged 40–70 years, an estimated 34.8% have moderate to complete erectile dysfunction (Porst, 2004). It has been recently estimated that more than 152 million men worldwide experienced erectile dysfunction (ED) in 1995, and that this number will rise by 170 million, to approximately 322 million by the year 2025 (Kandeel et al., 2001). Treatment of ED usually involves the psychotherapeutic approach. Pharmacotherapy involves locally acting vasoactive drugs such as papaverin and alprostadil (Bostandjiev and Mitra, 2004), and first-line oral therapy for ED includes phosphodiesterase type 5 (PDE-5) inhibitors such as sildenafil, vardenafil, and tadalafil, which inhibit hydrolysis of the second messenger cyclic guanosine monophosphate (cGMP), whose production is promoted by nitric oxide (NO) release within the penile smooth cells (Montorsi et al., 2006; Wespes et al., 2006). Central stimulants like apomorphine (Heaton, 2000; Montorsi et al., 2003) and herbal drugs with aphrodisiac activity are also involved in treatment of ED. Surgical interventions are also used, including insertion of penile prostheses (Bostandjiev and Mitra, 2004). The available drugs and treatments have limited efficacy, unpleasant side-effects such as headache, flushing, dyspepsia, nasal congestion and color visual disturbances with PDE-5

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inhibitors (Porst, 2004; Dhawan et al., 2003; Tharakan and Manyam, 2005) as well as contraindications in certain disease conditions. A variety of botanicals such as *Tribulus terrestris*, *Aframomum melegueta*, *Eurycoma longifolia*, *Cnidium monnieri*, *Ferula harmonis*, *Mucuna pruriens*, *Lepidium meyenii* and yohimbine as an alkaloid obtained from the bark of *Pausinystalia johimbe* (*Corynanthe yohimbe*) (Tharakan and Manyam, 2005), as well as *Passiflora incarnate* (Dhawan et al., 2003) are reported to have a potential effect on the sexual functions, supporting older claims and offering new hope (Tharakan and Manyam, 2005).

Crocus sativus L., commonly known as saffron, is a perennial stemless herb of the Iridaceae family that is widely cultivated in Iran and other countries, including India and Greece (Ríos et al., 1996). Commercial saffron comprises the dried red stigma with a small portion of the yellowish stamina 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 glycoside, crocin) (Ríos et al., 1996). In modern pharmacological studies, saffron or its active constituents have demonstrated anticonvulsant (Hosseinzadeh and Khosravan, 2002), antidepressant (Hosseinzadeh et al., 2004), anti-inflammatory and antinociceptive (Hosseinzadeh and Younesi, 2002) and antitumor activities (Abdullaev, 1993; Escribano et al., 1996). Radical scavenger effects as well as learning and memory-improving properties (Zhang et al., 1994; Abe et al., 1999) and promotion of the diffusion of oxygen in different tissues have also been reported (Ríos et al., 1996). Saffron extract is also chemopreventive and showed protective effects on genotoxin-induced oxidative stress in Swiss albino mice (Abdullaev et al., 2002; Nair et al., 1995; Premkumar et al., 2003). In traditional medicine, saffron is recommended as aphrodisiac agent (Madan et al., 1966). Thus, in this study the effects of saffron stigma extract and two active constituents, crocin and safranal, on sexual behaviors were evaluated in male rats.

Materials and methods

Animals

Virgin Wistar rats weighing 230 ± 10 g each were obtained from a random bred colony in the animal house of Mashhad University of Medical Sciences. Animals were housed in the colony room under a 12/12 h light/dark cycle at 21 ± 2 °C. Animals had free access to water and food. All animal experiments were carried out in accordance with Mashhad University of Medical Sciences, Ethical Committee Acts.

Plant material

Crocus sativus L. stigmata were collected from Ghaen (Khorasan province, Northeast of Iran). A voucher specimen was authenticated and deposited in the Herbarium of Faculty of Pharmacy, Mashhad University of Medical Sciences.

Quantification of crocin and safranal in saffron aqueous extract

To quantify crocin and safranal in an aqueous saffron extract, a modified method was used (Sujata et al., 1992; Hadizadeh et al., 2007). The extract of authentic stigmata was passed through a 0.2-μm Millipore filter (Millipore, Bedford, MA, USA) and eluted with 100% methanol. This 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 using Shimadzu Class-VP^{TM} 6.10 software (Hadizadeh et al., 2007).

Chemicals

Crocin and safranal were purchased from Fluka. Sildenafil was obtained from Poursina, IR Iran.

Preparation of extracts

40 g of stigma powder were macerated in 1500 ml water for 72 h. The mixture of plant and water was subsequently centrifuged (5 min, 3000 rpm) and the supernatants were evaporated to dryness under reduced pressure at 40 °C. The yield of the extract was 45% (w/w).

Treatment

Male rats were divided into 11 groups of 6 each. All agents were administered intraperitoneally. Rats of group I received 10 ml/kg body wt. normal saline as vehicle and served as negative control. Group II rats received sildenafil citrate at a dose of 60 mg/kg body wt. and served as the reference group. Rats from groups III, IV and V received saffron extracts at doses of 80, 160 and 320 mg/kg body wt., respectively. Rats from groups