

## Saffron Safety in Humans: Lessons from the Animal and Clinical Studies

Lymperopoulou CD and Lamari FN\*

Department of Pharmacy, University of Patras, 26504 Patras, Greece

\*Corresponding author: Lamari FN, Department of Pharmacy, University of Patras, 26504 Patras, Greece, Tel: +30-2610-962335; E-mail: [flam@upatras.gr](mailto:flam@upatras.gr)

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### Editorial

*Crocus sativus* L (known as saffron, , fân hóng huā) is a member of the Iridaceae family. This genus of *Crocus* includes roughly 90 different species originating from central and southern Europe, North Africa, Middle East, and central Asia to China. *Crocus sativus* is widely cultivated in the Mediterranean area and Middle East because of its widespread use as a spice. From the ancient years, dried styles (the upper parts are the stigmas) of the plant were used as a food additive for its yellowish color and bitter taste.

Except its use in gastronomy, saffron is used through the centuries as a medicinal plant; more than 90 medicinal uses have been recorded, especially for gynecologic and ocular disorders. Modern pharmacological studies have demonstrated that saffron stigma extracts are promising for the treatment of asthma, depression, dementia, hypertension, premenstrual syndrome, obesity, and diabetes; most have been performed in animals whereas small-scale clinical trials have also been reported in recent years [1-4].

One recurring concern about saffron medicinal use in humans is its safety. Dioscorides in *De Materia Medica* reports that saffron in the dose of three drachmas (about 12 g) is reportedly lethal. In *Pharmacopoeias* [5] and herbal monographs (that of German Commission E) toxic effects are reported with 5 g and above, and the lethal dose is said to be approximately 20 g; adverse effects include vomiting, uterine bleeding, bloody diarrhoea, haematuria, bleeding from the nose, lips and eyelids, vertigo, numbness and yellowing of the skin and mucous membranes. The effects on the uterus are in agreement with its past use as an abortifacient at doses >10 g.

However, those reports are old and the respective amounts have been in times questioned [6]; one possible reason is that its common name (saffron) has been also used to describe a poisonous plant, *Colchicum autumnales*. On the other hand, no one dares use such high doses of saffron in humans and many toxicity studies are performed in animals, but the results are sometimes not consistent and difficult to interpret in human doses.

Some animal and clinical studies use saffron suspension in water or saffron capsules and others, ethanolic or aqueous extracts, but in the majority of them the control of saffron quality is poor. Saffron quality depends on the presence and concentration of its three major style constituents: safranal (the main constituent of saffron's essential volatile oil responsible for odor and aroma of the herb), picrocrocin (responsible for the bitter taste of saffron) and crocins [various apocarotenoid (crocin) glycosides responsible for coloring properties of saffron] [7]. In agreement with previous studies, we have recently shown that the geographical origin, drying procedures, storage conditions and packaging have a great impact on the concentration of the bioactive principles in saffron samples [8]. Besides that, in order to aid the interpretation one should bear in mind that in many reports

(including our experience) the yield of the ethanolic extraction (usually 50-80% v/v) is about 50% of the crude dry plant material. Successful extraction can also be performed with water [9] but the conditions and the yield had better be described.

The route of administration also greatly affects the outcome of the efficacy and/or toxicity studies. The effective or toxic doses when saffron is administered intraperitoneally are lower than those required for the same result in oral administration studies. Ramadan et al. demonstrated that oral administration of the ethanolic extract of saffron in doses up to 5 g/kg B.W. (body weight) did not produce any demonstrable acute toxic effect or death in mice [10], whereas in the study of Mohajeri et al. the intraperitoneal median lethal dose (LD50) value of ethanolic extracts was 3.5 g/kg B.W in rats [11]. The adverse effects recorded in the latter study are the decrease of body weight and appetite, increase of white blood cells, normochromic-normocytic anemia, hepatic and renal dysfunction. The same adverse effects, but in a mild degree, were evident in mice that were exposed to two different doses of the ethanolic extract 4 and 5 g/Kg BW orally for five weeks [12]. The above results about the 5 g/kg oral doses suggest that saffron extract is considered practically not to have any acute toxic effect. Sub acute studies also showed that the oral administration of 500 mg/kg to rats for 8 weeks [10] did not produce any significant change in liver and kidney functions, whereas the intraperitoneal administration of >350 mg/kg ethanolic extract to rats for 14 days [11] affected the aforementioned biochemical parameters and caused hepatic and renal injury. Besides one study which used saffron suspension in water demonstrated oral LD50 value of 4120 ± 556 mg/kg in mice [13].

The direct conversion of animal doses to human doses is erroneous since it does not take into account the different physiology of the organisms [14]; the conversion based on body surface area has been suggested as a guide by researchers and regulatory authorities [15]. In that case, to convert a mouse or rat dose to human equivalent dose (HED in mg/kg) it is suggested to multiply the animal dose by 0.08 or 0.16, respectively. The application of this calculation to the study of Bahmani et al. [13] yields an equivalent oral LD50 of 20 g saffron for a 60 kg person. In addition, the interpretation of the intraperitoneal ethanolic extract LD50 of 3.5 g/kg in rats is estimated to be equivalent to lethal doses of 33.6 g dry extract or 67.2 g saffron for a 60 kg person. Although the absolute values differ and despite the differences in the route of administration, the values of lethal doses in humans are in agreement with those recorded in old herbal monographs.

Another great concern has been the effect of saffron administration to pregnant women and their neonates. To evaluate lactating toxicity in mice, saffron was administered orally to the mothers once daily for 21 days, after delivery, during lactating period at doses of 500 (HED of 2.5 g saffron/60 kg person), 1000 and 2000 mg/kg B.W and its administration did not have any toxic effect on liver [13]. However, histopathology changes were noticed in the kidney of neonates but the doses administered were quite high. In the study of Edamula et al.,

saffron administered in Wistar rats through an oral gavage from implantation (day 5 post coitus) through lactation up to lactation day 20 at the doses of 50 (HED 480 mg/60 kg), 250 and 1000 mg/kg/day did not induce any maternal toxicity or any toxicity on the developing fetus/pups including its survivability [16]. In agreement, saffron did not induce any maternal toxicity and fetal developmental toxicity in Wistar rats when it was administered orally daily by gavage during gestation days 5 to 19 up to the highest tested dose of 1000 mg/kg/day (HED of 9.6 g saffron/60 kg person) [17].

In the last decades many clinical trials have been conducted in order to determine the efficacy of saffron against severe diseases and identify possible side effects or toxicity. Alzheimer's disease is one of the first in which saffron's efficiency was investigated. Akhondzadeh et al. studied in two different clinical trials the effect of saffron treatment in mild-to-moderate Alzheimer's disease [18,19]. Capsules of 15 mg of saffron were administered twice a day for 16 weeks [18] or for 22 weeks twice a day [19]. In both studies no major side effects were observed and saffron's administered dosage was evaluated as safe.

In an evaluation of its antidepressant activities (capsules of 30 mg of saffron twice per day for 6 weeks) saffron had not significant different side effects compared with placebo [20] or fluoxetine [21] and imipramine [22]. Kermani et al. have studied the efficacy of saffron in metabolic syndrome [23]; they administered 100mg/day for 12 weeks and recorded the beneficial reduction of serum prooxidant-antioxidant balance and the safety of the treatment.

Another group of conditions in which treatment with saffron was evaluated are sexual dysfunctions. Erectile dysfunction was treated in a pilot study with 200 mg of saffron every morning for 10 days; no side effects were observed [24]. Many preclinical studies have shown that consumption of saffron decreases body weight and fatigue. Gout et al. showed that 1 capsule of Satiereal (176,5 mg extract of saffron) daily for 8 weeks may cause reduction of snacking frequency and demand [25] with no major side effects.

Saffron's safety was evaluated in a clinical study where healthy volunteers were treated with 200 and 400 mg tablets of saffron ethanolic extract for 1 week. The decrease of standing systolic BP and MBP and, also, the abnormal uterine bleeding in one female in each group of 200 and 400 mg were reported [26].

The above clinical studies show that saffron is absolutely safe and not toxic in the low doses used for the clinical studies. It is interesting that in our studies in rats and mice we used the 60 mg/kg B.W. dose of alcoholic extract, which was effective for the prevention of cataract (two times administration) and as a nootropic in aged and adult rats after a 7-day intraperitoneal administration [27]. The calculated HED (288 mg or 576 mg extract) appear to be not unattainable in humans; further safety studies are necessary to adjust the dose. In one recent study even 1 g per day did not cause any toxicity or serious side effects in participants after 8 weeks of administration, but a more thorough investigation is necessary [28].

In conclusion, saffron seems to have a wide therapeutic index and the pharmacological doses tested so far are safe. The toxic and lethal effects of saffron at high doses should not be forgotten but at the same time should not deter the therapeutic utilization of this medicinal herb.

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