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Saffron in phytotherapy: Pharmacology and clinical uses

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Safran in der Phytotherapie: Pharmakologie und klinische Verwendung

Zusammenfassung. Safran (Stigmata von *Crocus sativus* L.) wird seit Jahrtausenden für medizinische Zwecke verwendet. Im Verlauf der Geschichte lässt sich regelmäßig die Verwendung gegen Krebsleiden und bei depressiver Verstimmung identifizieren. Diese Anwendungen waren auch Schwerpunkt der modernen Forschung. Vielversprechende und selektive Effekte gegen Krebs wurden *in vitro* und *in vivo* beobachtet, während antidepressive Effekte sowohl *in vivo* als auch in klinischen Pilotstudien bestätigt wurden. Safranextrakte haben daher das Potenzial, einen wesentlichen Beitrag zur rationalen Phytotherapie zu leisten.

Schlüsselwörter: *Crocus sativus*, Pharmakologie, klinische Verwendung, Depression, Krebs.

Summary. Saffron (stigmates of *Crocus sativus* L.) has been used for medicinal purposes for millenaries. Throughout history, uses against cancer and depressive mood can regularly be identified. These applications have also been in the focus of modern research. Promising and selective anti-cancer effects have been observed *in vitro* and *in vivo*, but not yet in clinical trials. Antidepressant effects were found *in vivo* and in clinical pilot studies. Saffron extracts thus have the potential to make a major contribution to rational phytotherapy.

Key words: *Crocus sativus*, pharmacology, clinical application, depression, cancer.

Introduction

Saffron is the vernacular name for the stigmata from the flowers of *Crocus sativus* L. (Iridaceae). *Crocus* is a Mediterranean plant won predominantly by cultivation. The area where *Crocus sativus* is grown spreads from the Mediterranean Sea through Persia to India, Tibet and China. Relatively new cultivations have been created in Mexico and Australia.

The world's total annual saffron production is estimated at 205 tons per year, with >80% of this harvest originating from Iran, mainly from the Khorassan province [1, 2]. Within Europe, Spain is generally believed to be the major source of cultivated *Crocus sativus*, based on an annual export of approximately 60 tons. However, since the collection of saffron is a very costly and time-consuming procedure, the bulk of saffron re-exported from Spain is in fact of Iranian and Moroccan origin. In fact, the largest European saffron producer is currently Greece with 4.5 tons/year, a figure which according to data from the 2nd International Symposium on Saffron biology and technology (Mashhad, Iran, October 28–30) has remained stable in the past years, and by far surpasses the current Spanish production.

The decline of European saffron seems to be closely related to the high labour costs involved in saffron production. The re-exporting and re-labelling of saffron probably contributes to the finding of a relatively uniform quality of saffron independent of the labelled origin [3]. Adulterations are frequent: At least 30% of saffron samples do not fulfill quality specifications or are to be considered as waste products or even a non-saffron product [3].

Collection time is in autumn, when the flowers are opening. Flowers are picked in the early morning, and the stigmata are manually removed and dried. The quantity of flowers needed to produce 1 kg of saffron varies between 150,000 and 200.000. Traditional saffron production is still mainly family-based work, although GMP conform production is now emerging.

Uses

Saffron was not always primarily a spice, but rather a highly valued medicinal plant, for which many uses have been reported. Saffron is traditionally used against

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Fig. 1. Traditional saffron production in Khorassan (Iran): Flowers are manually collected and sold by the kilogram to families who manually remove the stigmata. The dry material is then sold to spice shops, who deliver to wholesalers.

cramps, asthma and bronchospasms, menstruation disorders, liver disease and pain. Its use for cramps and asthma was negatively evaluated by the German Commission E. Saffron was also said to have a soothing and tonifying effect on the gastrointestinal tract [4]. A major use, however, is and was the application as a stimulant, aphrodisiac and antidepressant [4–8]. The use as an adaptogen is documented in Indian Ayurvedic medicine. Another typical application is in supportive treatment of various forms of cancer. The latter effects, especially the antidepressant and tumour-protective effects, have been confirmed in pharmacological experiments [9].

Chemical composition and quality aspects

Quality saffron is characterized by its typical combination of bitter taste, aromatic smell and intense red colour. Its bitter taste originates from picrocrocin, a β-D-glucoside of hydroxysafranal [10]. During processing of the fresh plant material, picrocrocin converts into the tasty safranal by thermic or enzymatic degradation. Other trace compounds, mostly monoterpenoids from the volatile fraction additionally effect the aroma, many of them being secondary degradation products from non-volatile compounds [10]. The harvesting and drying process may strongly affect the taste and flavour of saffron. Its colour, obvious at already very high dilutions, originates from the crocins, glycosides of the carotenoid crocetin with various sugar ester moieties. Besides the crocins, other minor carotenoids are present in saffron. Good quality saffron contains about 30% (!) of crocins, 5 to 15% of picrocrocin and usually up to 2.5% of volatile compounds including safranal. Extracts from saffron can, however, be aimed at a selected fraction, according to the intended use. Aqueous saffron extracts designed for the use as an antidepressant contain 5% safranal and more.

Because of the complex spectrum of a variety of ingredients responsible for saffron quality a very detailed quality assurance of the raw material is a prerequisite, especially when it comes to the reproducibility of saffron preparations for clinical application. A minimum requirement is the analytical determination of picrocrocin, safranal and total crocins.

Pharmacology

Anti-tumour-Effects

Anti-tumour effects have been evidenced in various cellular models, and have been extensively reviewed [9, 11]. The viability of healthy cells regularly remained unaffected, whereas saffron had selective cytotoxic effects on malignous cells, including human cancer cell lines, with effective doses in the low micromolar range. Whereas dose-dependent inhibition of colony formation was found in tumour cells, proliferation and differentiation of healthy cells remained unaffected.

Orally and topically applied saffron extracts reduced the incidence of artificially induced cancer *in vivo*, inhibited tumour growth rates and prolonged the life span of the test animals [12, 13]. Moreover, the toxicity of cytostatic drugs such as cisplatin was reduced in animal models of cancer treatment [12, 14–17].

Aqueous saffron extract antagonized the reduction of GSH-levels and other protective enzyme systems in animals with cancer treated with cytostatics [18]. Isolated crocetin protected rat liver cells from the damaging

impact of aflatoxins [19]. At the same time saffron was essentially non-toxic in mice, with an LD_{50} of 600 mg extract/kg body weight [12]. A recently found affinity of saffron extract and the isolated crocins to the sigma-1 receptor (IC_{50} 30µM) may explain some of the described anti-tumour effects [3].

Anti-inflammatory effects

Hosseinzadeh und Younesi (2002) tested the anti-inflammatory effects of aqueous and ethanolic extracts from saffron and *Crocus* flowers in mice, using the hot plate and writhing tests. Whereas no effect was found in the hot plate test, the stigmata inhibited the acetic acid induced writhing reflex. The effect could only partially be inhibited by naloxon [20].

Improvement of learning abilities and memory

The oral application of 125–500 mg/kg of saffron extract to mice had no effect on learning abilities in the passive avoidance test, but distinctly improved the memory of mice pre-damaged with ethanol [21]. This effect could be attributed to crocin, which does not have an effect in a dose range of 50–200 mg in healthy animals, but in fact improves cognitive functions in animals where memory was artificially impaired by application of ethanol [22, 23].

Antidepressive effects

Intraperitoneally applied aqueous and ethanolic extracts of saffron and its constituents safranal and crocin were shown to have antidepressant effects in mice, using the forced swimming test. Immobility time was decreased by saffron extracts in a dose of 200–800 mg/kg, and by safranal (0.15–0.5 mg/kg) and crocin (50–600 mg/kg). Safranal increased swimming time. Climbing time (which is increased by imipramin) is increased by both extracts, safranal (0.5 mg/kg) and crocin (50–600 mg/kg). In the open field test, the ethanolic extract and safranal increased stereotypic behaviour. Safranal and crocin both contribute to the antidepressant effect, with crocin probably acting via re-uptake inhibition of dopamine and norepinephrine, and safranal via serotonin reuptake inhibition [24, 25]. *In vitro,* crocin was found to have a weak, but significant affinity to the NMDA receptor (IC_{50} 10 µM) [3] and to antagonize ethanol-induced depression via NMDA-receptor [26].

Clinical use

Experience from clinical studies is limited to four pilot trials, three of which were designed to demonstrate the antidepressant efficacy of saffron extracts.

Daily intake of 100 mg of saffron in milk for 6 weeks led to an improvement of the antioxidative status of patients with coronary heart disease. 10 healthy volunteers and 10 patients received saffron, whereas 10 patients with ingestion of milk only served as controls [27]. The susceptibility of lipoproteins to oxidation decreased considerably in the patients (–35.8%) as well as in the healthy volunteers (–42.3%), whereas no change was found in controls (increase to 103.6%) [27].

In a clinical double-blind study, 30 patients with mild to moderate depression (HAMD > 18) were either treated with 30 mg of saffron or with 100 mg of imipramine for 6 weeks. The effects were found to be equivalent, with a better tolerability of saffron [28]. This pilot study was followed by a placebo-controlled trial in 40 patients suffering from depression. Saffron was found to be significantly superior to placebo [5].

In a six-week randomized, double-blind pilot study, Noorbala et al. (2005) compared the efficacy of an aqueous-ethanolic saffron extract (30 mg/day) with that of fluoxetine (20 mg/day) in 40 outpatients with mild to moderate depression. The equivalence of both treatments was confirmed [29].

The trials on depression confirm the observations from *in vivo* pharmacological studies. However, a full size trial with a design corresponding to the most recent guidelines on depression therapy is needed for a definite conclusion. Still, it is noteworthy that saffron's use against depressive symptoms has a long tradition from antiquity to date. In the countries of origin, saffron tea has the reputation of improving mood – which may well be in line with antidepressant effects. Further research into the use in depression seems worthwhile.

Safety

Reports on toxicology and safety are at best confusing. Daily doses of up to 1.5 g of saffron are thought to be safe. Since the dose shown to be efficacious in depression trials corresponded to approximately 30 mg of saffron, there is a large safety margin. Toxic effects are reported with 5 g and above, with a lethal dose of approximately 20 g. Reportedly, saffron has been used for the induction of abortion in doses > 10 g. This dose is said to cause vomiting, uterus bleeding, haematuria, bleedings of the gastrointestinal mucosas as well as vertigo and dizziness. The coloured constituents may accumulate in sclera, skin or mucosas, and may thus mimic icteric complaints [4].

Descriptions of adverse effects are mostly found in the older literature (prior to 1925). According to these sources, nausea and revulsion was described in doses between 1.2 g and 2 g – followed by vomiting, diarrhoea and bleeding. Apparently there was no dose-adverse effect correlation. In some cases the ingestion of 4 g of saffron per day for several days did not cause any adverse events even in pregnant women, whereas this same dose was reported lethal in other cases. This striking discrepancy might be due to the causative agent in the reports of adverse events not being saffron, but rather a substitution such as "meadow saffron", *Colchicum autumnale*. In addition, many such cases were reported from Germany [30], where saffron is not a typical crop, whereas *Colchicum autumnale* is relatively abundant.

Saffron and saffron extracts were found to have a very low or even non-existent toxicity in *in vivo* studies in animals [25, 30, 31].

One case of an anaphylactic reaction to saffron has been reported [32]. Lucas et al. (2001) assessed the allergenic risk of saffron as very low. In view of the annual production of > 200 tons of saffron, allergic reactions to

saffron can be expected to occur in only very rare cases [33], which has also been confirmed by the analysis of 589 prick tests on allergies against various spices [34].

Conclusions

Modern pharmacological research and starting clinical testing confirm large parts of traditional knowledge regarding the medicinal effects of saffron. Currently, pharmacological research focuses on anti-tumour effects, whereas clinical testing has provided evidence for the traditionally well-known antidepressant effects. With the recent availability of aqueous extracts with reproducible composition and preparation according to pharmacopoeial standards, the foundations for a development of saffron extracts into rational phytomedicines have been laid.

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