Saffron (*Crocus sativus*):
An evaluation of the scientific literature

Version of May 18, 2006[1]

A joint project of

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[1] This evaluation is primarily based on the analysis of citations. As there are often distinct differences between citations and the original publication, corrections and amendments have to be expected on evaluation of the original papers.

Table of Contents

Saffron is the vernacular name for the stigmates from the flowers of *Crocus sativus* L. (Iridaceae). Safran is exclusively obtained from cultivation.

Botanical Backgrounds and History

The genus *Crocus* consists of approximately 80 different species (ca 135 taxa). A typical feature of the genus is the long, thin flower tube with three stamina and a filiform stigmate split into three endings. The form of the stigmates is a botanical characteristic for the differentiation of species.

Flower of *Crocus sativus*: The three red stigmates are the material from which saffron is obtained.

Crocus is a Mediterranean plant predominantly from cultivation. The area of repartition of *Crocus sativus* spreads from the Mediterranean sea over Persia to India. *Crocus sativus* respectively the stigmates depicted as saffron have been known and savoured since antiquity. The name „Crocus“ is eventually derived from the old Hebrew word „Carcom“, whereas the name „Safran“ can be ethymologically traced back to the Arabian word „safra“ = yellow and Persian „za-faran“, and thence to the Babylonic word „azupiru“.

Synonyms for *Crocus sativus* are *Crocus autumnalis* S.M. and *Crocus officinalis* MARTYN. The use of the name *Crocus autumnalis* is especially unfortunate, as in the past a number of confusions with “meadow saffron” (*Colchicum autumnale*) and corresponding cases of toxicity after collection of naturally growing flowers have been reported. Such accidental confusions are excluded when *Crocus sativus* from cultivation is used as raw material.

Within Europe, Spain is believed to be the major source of cultivated *Crocus sativus*. Even though there are cultivations in the regions of Alicante, Albacete, Ciudad Real, La Mancha, Mancha Real, Murcia, Teruel, Toledo and Valencia, there is a discrepancy between the relatively small scale cultivation in Spain and the market demands, respectively the traded quantities of raw material. A closer look at the commercial channels reveals that a large part of the saffron labelled as „Spanish“ in fact comes from Persia, and explicitly from Iran, and more specifically from the region of Khorassan.

Cultivation and Propagation

The propagation in callus cultures was described and optimized for the production of crocin with the use of plant hormones. The maximum production of crocin was 0.43 g/l. The yield of crocin could be further increased to 90 mg/l by the addition of the rare-earth elements La^{3+} and Ce^{3+}.

The formation of crocetin glycosides was likewise studied in callus cultures.

Callus cultures were also made starting from the cormlets, and optimized for the production of an immunomodulatory active proteoglycane.

In vitro-cultures can be no replacement for the cultivation of Crocus, as there are distinct qualitative and quantitative differences in the phytochemical composition between real saffron and in vitro-cultures.

Cultivation of *Crocus sativus*

Herbal raw material

Collecting saffron stigmates is still a very costly and time-consuming procedure. Collection time is in autumn, when the flowers are opening. The flowers just opening are picked in the early morning, and the stylus including the stigmates is manually removed. The harvesting has to happen within two days after the first opening of the flowers, as otherwise the flowers will wither. The collected stigmates are spread on hair sieves and dried. In the drying process the characteristic odour develops.

Collection of Crocus flowers

Manual removal of saffron stigmates

Various drying methods have been compared: drying at ambient temperature, with hot air, and drying with methods traditionally used in Spain (charcoal, gas or electrical heating).

Safranal is the compound responsible for the aroma of saffron. Together with crocin derivatives, safranal is a quality biomarker for saffron used as a spice. The handling of the stigmates clearly has an influence on the content of these compounds.

The quantities of flowers needed to produce 1 kg of saffron vary between 150,000 and 220,000. This distinct variation is due to the fact that a good quality of saffron requires a careful selection of flowers with an appropriate quality, and to the fact that only a part of the stigmates is used for the best qualities.

Generally, three different qualities are distinguished for saffron:

- The complete stylus with dark red stigma and a yellowish filament.
- The separated dark red stigmata. Best quality in respect to colour and aroma, but highly expensive.
- The separated yellowish filaments. Relatively cheap and aromatic.

The three qualities are distinguished in their organoleptic characteristics as well as their costs. The red stigmata are considered the most valuable parts of saffron.

The red parts of the stigmates are considered having the best quality.

Left: Freshly picked stigmata including the white part. Right: Saffron traders in Mashhad (Khorassan).

The typical organoleptic characteristics of saffron are colour, aroma and taste. Due to the high costs of saffron, adulterations are a typical and quite frequent phenomenon. In a screening experiment 44 out of 47 commercial samples were shown to be adulterated; in another examination unacceptable foreign material was found in 90% of 151 samples. Powdered material is more frequently adulterated than whole saffron.

As a typical adulteration the stigmates from other *Crocus* species are mixed into the herbal material, partly after red colouring with aniline dyes to correct deviations in colour. Alternatively pre-extracted saffron is traded. This type of saffron is betrayed by its light colour and the lack of colouring potency. Again, the material is partly treated with dyes. Further adulterations are flowers of other species cut to stripes, such as *Calendula officinalis* L., *Carthamus tinctorius L.*, *Onopordon acanthium* L., *Cynara cardunculus* L., *Zea mays* (the stigmates), *Crocosmia aurea* POPPE ex HOOK (Cape saffron), *Arnica montana* L., *Scolymus hispanicus* L., *Papaver rhoeas* L., *Punica granatum* L., *Sutera atropurpurea*, *Crocosmia crocosmiflora* LEMOINE, rootlets of various Allium species (*Allium schoenoprasum*, *Allium porrum* L.), the outer leafs of onions, stamina of a non-identified type of carnation, Capsicum powder up to 70% in the saffron powder, cut and dyed grassy plants, powdered sandal- and campech wood, Curcuma powder or vetch seedlings. These adulterants are partly produced using industrial methods. Adulterants of animal or synthetic origin include dyed gelatine fibres, meat fibres from salted or dried meat, and synthetic dyes.

Typical additions to increase the weight of the commercial material are water, syrup, glycerol, honey or fatty oils. Lycopodium powder is added to avoid the sticking together of the stigmates. Alternatively the addition of inorganic salts such as calcium carbonate, barium sulphate, magnesium sulphate, potassium nitrate, potassium carbonate or borax was observed.

Analytical procedures were developed for the detection of adulterants. E.g., a fingerprint GC-MS analysis of 252 samples of Spanish saffron was published. Others authors used methods of gene analysis to demonstrate an adulteration with *Carthamus tinctorius* L., *Hemerocallis fulva* L., and *Hemerocallis citrina* BARONI. The latter plants count among the most typical adulterants in China.

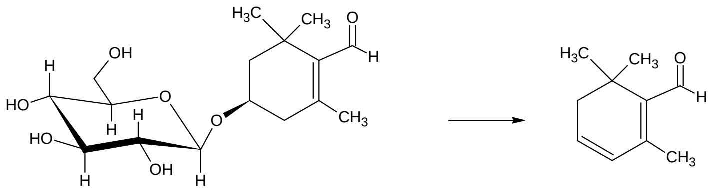
Chromatographic and spetrophotometric methods for the detection of synthetic dyes such as naphthol yellow, tatrazine, quinoline yellow, Sunset yellow, Allura red, amaranth, azorubine, Ponceau 4R and Red 2G in saffron were presented. Erythrosine and carminic acid cannot be evidenced with this method.

A special type of impurity is the irradiation of saffron with x-rays. An irradiation can be demonstrated though the analysis of the fragmentation pattern of the carotenoids.

Calendula officinalis, one of the more frequent adulterants of saffron.

Constituents

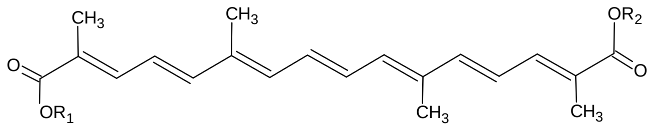
Saffron contains 0.4 to 1.3% of essential oil with *α*- und *β*-pinene, 1,8-cineol and safranal as the major component. Safranal is responsible for the typical aroma of saffron. The picrocrocin content of fresh saffron can be up to 4%, whereas this constituent is usually not present in well-stored saffron. In addition, the herbal substance contains hydroxysafranal, 2-phenylethanol, the isophoron 3,5,5-trimethylcyclohexenon and various other isophorons.



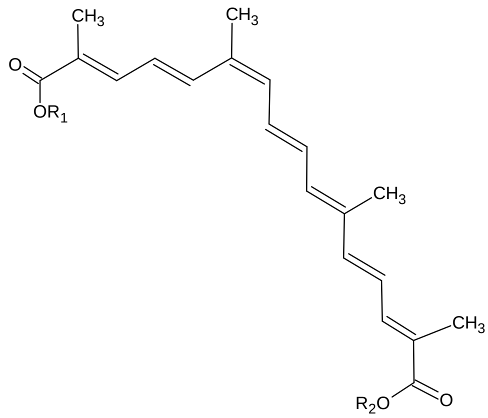
Picrocrocin Safranal

Safranal derivatives can be carefully extracted by means of supercritical CO_2, followed by HPLC/GC-analysis. Another HPLC method for the separation of safranal, crocin isomers and picrocrocin was described.

Constituents of saffron responsible for the colour are the yellow-red crocins, present in a quantity of ≤ 2% of the dry weight. The coloured compounds are mono- and diglycosides of the water insoluble, brick-red polyene dicarbonic acid crocetin (8,8′-diapocarotin-8,8′-dicarbonic acid). The good solubility of these carotenoid dyes in water is caused by carbohydrate units condensed to the backbone. Traces of free crocetin (*α*-crocetin), methyl crocetin (monomethyl ester of *α*-crocetin = *β*-crocetin) and *trans*-dimethyl crocetin (*γ*-crocetin) can be evidenced. Furthermore saffron contains small amounts of “normal” carotinoids, such as *α*-, *β*- and *γ*-carotin, lycopin and zeaxanthin.



all-trans-Crocin



13-cis-Crocin

	R_1	R_2
A-Crocin	β-D-Gentiobiose	β-D-Gentiobiose
B-Crocin	β-D-Gentiobiose	β-D-Glucose
C-Crocin	β-D-Gentiobiose	H
D-Crocin	β-D-Glucose	β-D-Glucose
E-Crocin	β-D-Glucose	H
Dimethylcrocetin	CH_3	CH_3
Crocetin	H	H

Crocins and crocetin can be simultaneously quantified by HPLC or by capillary electrophoresis. The carotenoid glucosides from saffron react sensitive to light, oxygen and betaglucosidases, and are potentially unstable.

With approximately 0.01% of the dry weight, saffron counts among the richest sources of vitamin B_2. Furthermore the drug substance contains up to 7% of fatty oils (glycerol esters of palmitic, stearic, lauric and oleic acid).

Next to 21 further compounds, various crocusatins were identified in saffron.

Uses

Reagents prepared from saffron are used in medicine for special histological dying techniques.

The dying potency is also an important feature in cosmetology. Crocin derivatives are registered carotenoid dyes.

Due to an assumed synergism between saffron and minoxidil, a combination of 5 % saffron and 0.5 % minoxidil is used as a hair growth agent (Japanese patent).

The use of saffron as a spice dates back to the crusades of the 12th Century. Saffron is still widely used as a spice for rice dishes, consommé, and fish recipes in Mediterranean countries and the Middle East. In Europe much saffron went into the production of various alcoholic bitters, and was used as a dye in baking cakes and pastry (as in the German child's song: "Safran macht den Kuchen gehl" = Saffron makes the cake yellow). Since there are cheap synthetic dyes this type of use has strongly declined.

From traditional medicine many uses are known for saffron:

- Nervine
- Melancholia and hysteria
- Depression in Persian traditional medicine
- Cramps
- Asthma
- Cough and bronchospasms
- Expectorant
- Menstruation disorders (amenorrhea, dysmenorrhea, leucorrhea)
- Soothing and tonifying the gastrointestinal tract in dyspeptic disorders
- Carminative
- Fever
- Liver damage
- Anaemia
- Rheumatism, neuralgia, toothache
- Septic inflammations
- Supportive treatment of various forms of cancer, e.g. abdominal tumours, cancer of bladder, ears, kidneys, liver, neck, spleen, stomach, breast, mouth and uterus
- Stimulant and aphrodisiac
- Stimulation of circulation in Traditional Chinese Medicine
- Prevention of premature ejaculation (German patent of 1975 with a combination product).

The use in the treatment of diseases of heart, blood and eyes is described, as well as against muscular paralysis.

The discovery of adaptogenic and stress relieving properties might be of interest in view of the mentioned stimulating and aphrodisiac effects. The use of an adaptogen is documented in Indian Ayurvedic medicine. Significant anti-stress effects and anxiolytic properties have been evidenced in animal experiments and human application. A xanthon derivative called mangicrocin was isolated. Orally applied, mangicrocin was said to have shown adaptogenic effects in various test models. The effect was attributed to the xanthone moiety (mangiferin), but not to the carotenoid moiety (crocetin).

Regulations

In Germany, the trading of saffron is not restricted to pharmacies. The German commission E created a negative monograph for the indications „cramps“ and „asthma“.

Pharmacology

A number of effects of saffron extracts was examined in pharmacological test models.

Anti-tumour-Effects

Evidenced in various cellular models. The viability of healthy cells remained unaffected. Saffron extracts do obviously not convey a direct cytotoxicity. The fraction of crocetin was made responsible for the effects on tumour cells.

Cytotoxic effects were found in human cancer cell lines *in vitro*, with an ED_{50} ranging between 7 and 14 µg/ml of saffron extract. According to the researchers topically applied saffron extract inhibited the formation of artificially induced papilloma in a dose of 100 mg/kg. Oral application of saffron extract reduced the incidence of tumours. At the same time, the toxicity of cyclophosphamide was reduced.

In further examinations with more tumour cell lines saffron extract gave ED_{50}-values between 9 and 30 µg/ml. A dose-dependent growth inhibition of various implanted tumours was evidenced in mice, as well as a prolongation of the life span of the animals. Saffron was essentially non-toxic in mice, with an LD_{50} of 600 mg extract/kg body weight. It had no effect on healthy spleen cells. Oral application of saffron extract doubled the life span of cisplatin-treated mice, and reduced the typical adverse effects of chemotherapy, such as changes of haematologic parameters and weight loss.

The colony formation of tumour cells was dose-dependently inhibited by saffron extract, but not the colony formation of healthy cells.

As compared with controls, a significant anti-tumour effect on Sarkoma-180 and Ehrlich-Ascites cells in mice was found. In the presence of phytohemagglutinins saffron stimulated the unspecific proliferation of lymphocytes.

The saffron constituent crocetin reduced the kidney and liver toxicity of cyclophosphamide, and increased the GSH levels reduced under the influence of cyclophosphamide in the bladder.

The anti-tumoral effect was attributed to the constituent crocetin (among others), which inhibited the DNA and protein synthesis on malign cultivated cells when applied in isolated form.

The growth of HeLa2 cells was halfmaximally inhibited by 2.3 mg of an ethanolic saffron extract. Crocin and picrocrocin had an IC_{50} of 3mM, safranal even of 0.8 mM. Crocetin had no effect. Due to the good solubility in water the authors regarded crocin as the better candidate for the development of a cancer protective preparation.

A strongly cytotoxic proteoglycane was isolated from the corms of *Crocus sativus*. In non-toxic concentrations this proteoglycane led to a distinct activation of macrophages, protein kinase C and NF-κB *in vito*, and finally triggered apoptotic mechanisms of the macrophages, a finding supporting the hypothesis of immunomodulatory effects. The proteoglycane inhibits the growth of HeLa cells *in vitro*, as well as the growth of other human cancer cell lines (e.g. fibrosarcoma, cervical epithelioid carcinoma and breast carcinoma) with IC_{50}-values of 7-22 µg/ml. The toxicity of the proteoglycane was 8 times higher in malignant cells than in healthy cells. Normal erythrocytes show a 50% lysis only at 100 µg/ml, and 320 µg/ml induced a 60% cell death in human hair follicles.

On subcutaneous long-term treatment with 400 mg/kg of crocetin a prolongation of the life span of female, but not of male rats with colon carcinoma was observed. The effect was not accompanied by a relevant toxicity. *In vitro* cytotoxicity was evidenced in various cancer cell lines.

The saffron constituent crocetin was shown to be cytotoxic in human rhabdomyosarkoma cells in a dose range of 5-20 µg/l. In contrast to the effects of cisplatin cytotoxicity was only observed in malignant cells, but not in African Green Monkey kidney cells used as healthy controls.

The influence of saffron on the genotoxicity of cisplatin, cyclophosphamide, mitomycin and urethane was tested in mice. Animals were treated over five days with different dosage schemes (20, 40 and 80 mg/kg body weight) of an aqueous saffron extract. Genotoxicity was determined in the bone marrow micronucleus test. Pre-treatment with saffron inhibited genotoxicity, however, there was no clear dose-dependency. In saffron treated animals the GSH levels did not drop with the application of the cytostatics, whereas the levels decreased in the control groups without application of saffron. There were similar findings with other anti-oxidative enzyme systems. The anti-genotoxic findings were reproduced in a second series of experiments with up to 100 mg/kg of an aqueous saffron extract. The combined application with garlic or curcuma reinforced the effects.

In the colony formation test saffron inhibited malign cell types. All isolated carotenoids and especially crocin were shown to be cytotoxic in tumour cells.

With aqueous saffron extract a protective effect against DMBA/croton oil induced skin cancer of the rat was demonstrated.

The influence of carotenoids from saffron on H1-DNA-interaction was examined as a possible mechanism of action of the cancer preventive activity. The interaction of crocin, crocetin and dimethylcrocetin was measured by spectrophotometric methods. These substances inhibited the interaction of H1 and DNA, an observation pointing to a changed transcription on the level of the genes.

Cell-protective effects

Demonstrated in liver cells, among others. Crocetin protects rat liver cells from toxic effects of aflatoxins.

Reduced toxicity of cytostatics

Demonstrated in animal experiments.

The intravenous application of 50 mg/kg of saffron extract protected rats from cisplatin induced nephrotoxicity.

Improvement of learning abilities and memory

Found in pre-damaged animals. The effects on learning abilities and memory are due to crocin.

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.

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 does have an effect in animals where memory was artificially impaired by application of ethanol. Picrocrocin had no effect.

Crocin antagonizes the inhibitory effect of ethanol and acetaldehyde on long term potentiation in the hippocampus of rats *in vivo* and *in vitro*.

Antidepressive effects

In a pharmacological study the activity profile of a combination from red ginseng, saffron, *Polygala* root, antelope horn and aloe wood was examined. The combination increased the swimming time in the forced swimming test in rats. The application of 100 mg and more suppressed the formation of stomach ulcers in the model of the immobilized rat, respectively the water immersion stress test. Furthermore the combination prolonged hexobarbital induced sleeping time and reduced spontaneous activity. An attribution of single effects to saffron is not possible due to the complex combination. However, the antidepressive effects found in other examinations are in line with the test results.

Anti-Parkinson effects

In a rat model of Parkinson pre-treatment with crocetin did not lead to a loss of dopamin or GSH in the striatum and the *Substantia nigra*, whereas the content of TBARS decreased. Whilst the activity of antioxidant enzymes decreased in the control group, it remained constant under application of crocetin. These results were confirmed by histological observations in the *Substantia nigra*. The findings allow the conclusion of a potential usefulness of crocetin in patients with Morbus Parkinson.

Antioxidant effects

Saffron and its constituents possess antioxidant properties. In this context crocetin and crocin are mentioned.

The antioxidant effects of saffron respectively of crocin are used for the determination of the total antioxidant capacity of plasma: the decolouration of crocin correlates with the content of free radicals.

Anti-inflammatory effects

The anti-inflammatory effects of aqueous and ethanolic extracts from saffron and *Crocus* flowers were tested in mice, using the hot plate and writhing tests. No effect was found in the hot plate test. In contrast, the stigmates inhibited the acetic acid induced writhing reflex. The effect could only partially be inhibited by naloxon.

Inhibitory effects of a combination from red ginseng, saffron, polygala root, antelope horn and aloe wood were found in the model of the carrageenan-induced rat paw oedema, respectively in the model of histamine induced stomach ulcer. An attribution of the overall effect to single components is not possible due to the complex combination.

Blood lipid lowering effects

The crocetin fraction was made responsible for the blood lipid lowering effects.

Lipid lowering effects were evidenced in rats fed with cholesterol for 2 months. Crocetin led to a reduction of cholesterol, triglycerides and LDL, and to an increase of HDL cholesterol in blood serum. In addition, an inhibition of the proliferation of aortic smooth muscle cells was observed *in vitro*.

Promoting effects on wound healing

Corresponding hints can be found in the literature, but could as yet not be evaluated for this analysis.

Effects on heart and circulation

Saffron causes a cardiovascular stimulation, enhances circulation and lowers elevated blood pressure.

The effect of crocetin was examined in a model of tissue oxygenation of the hemorraged rat. No difference was found between saffron and saline treated rats for the average values of arterial pressure, oxygen and carbon dioxide partial pressure, pH and hematocrit. In contrast, the oxygen partial pressure in brain tissue was increased, which points to an improved tissue oxygenation in damaged areas under the influence of crocetin.

Under the influence of crocins increased circulation of the retina and an improved blood flow in the ischemic retina was found.

Aqueous and aqueous-ethanolic extracts from the flowers of *Crocus sativus* lower blood pressure in rats. 50 mg/100 g body weight of the aqueous extract lowered the artificially raised blood pressure from 133.5 ± 3.9 to 117 ± 2.1 mm Hg.

Crocetin has protective effects in adrenalin treated myocytes, expressed in lower values of lactate dihydrogenase in the culture medium, as well as in an increased activity of ATPase.

Spasmolytic effecs

Contractions of the *Vas deferens* of the rat and the ileum of the guinea pig caused by electrostimulation were inhibited by aqueous and aqueous-ethanolic extracts from the flowers of *Crocus sativus*. The aqueous extract inhibited the noradrenalin induced contraction of the *Vas deferens*, but not the KCl induced contraction.

Effects on the immune system

Saffron ameliorates the immune status.

Immunostimulating effects are mainly attributed to mangiferin.

Effects on blood clotting

Compounds with stimulating as well as inhibiting effects on platelet aggregation were found in the corms of *Crocus*.

Antiallergic effects

Crocin inhibits the calcium influx and the increase of calcium in the endoplasmatic reticulum of bovine smooth muscular cells.

Pharmacokinetics

Orally applied crocetin is quickly absorbed by mice, and can be detected in plasma in free form as well as in the form of a glucuronic acid conjugate (mono- and diglucuronates). The same metabolites are found on oral application of crocin.

The AUC after oral dosing of crocetin was determined in rats by means of HPLC. Crocetin is quickly absorbed. With a single dose of 50 mg/kg (10 rats) the authors obtained the parameters $t½\alpha$ = 30 ± 6 min, T_{max} = 65 ± 16 min, C_{max} = 5.0 ± 1.0 µg/ml, AUC = 845 ± 109) µg×min/ml, V_d = 5.0 ± 0.8 l/kg.

In the scope of pharmacokinetic examinations an HPLC method for the quantification of Crocin-1 in rabbit plasma was developed. After intravenous dosing the concentration-time-curve corresponded to an open 2-compartment model.

Clinical use

The antioxidant properties of a six week intake of 100 mg of saffron per day in milk were tested in 10 healthy volunteers and 10 patients with coronary heart disease. 10 patients with ingestion of pure milk served as controls. 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%).

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 imipramin for 6 weeks. The effects were found to be equivalent, with a better tolerability of saffron. This pilot study was followed by a placebo-controlled trial in 40 patients suffering from depression. Saffron was found to be significantly superior over placebo.

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

Toxicology and Pharmacovigilance

Daily doses of up to 1.5 g are thought to be safe. According to the monograph of the German commission E high doses (5 g and above) are toxic, with a lethal dose of approximately 20 g. With the ingestion of 5 g adverse effects such as purpura, thrombocytopenia and hypothrombinaemia were supposedly observed. Further reported adverse events observed with high saffron doses (for abortive uses in doses > 10 g) are vomiting, uterus bleeding, bloody diarrhea, haematuria, bleedings of the gastrointestinal mucosas, vertigo and dizziness. The coloured constituents may accumulate in sclera, skin or mucosas, and may thus mimic icteric complaints.

High doses of saffron extract are thought to have abortive properties (monograph of the German Commission E), an indication probably derived from the as yet unconfirmed observation of rhythmic contractions of the isolated uterus under the influence of fluid extract from saffron (as stated in a textbook on poisonous plants from 1925).

Descriptions of adverse effects are mostly found in the older literature (prior to 1925), and are potentially caused by adulterants or mislabellings, such as the use of “meadow saffron”, *Colchicum autumnale*, which may well account for some discrepancies between the lack of toxicity in studies with identified material, and spontaneous reports of toxicity of doubtful quality. According to the sources, nausea and revulsion was described with doses between 1.2 g and 2 g – followed by vomiting, diarrhea, bleedings, occasional triggering of menstruation, and uterus bleedings – which may well have been caused by *Colchicum*. Apparently there was no correlation between dos and adverse event. 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. Again, this striking discrepancy might be due to the causative agent in the reports of adverse events not being saffron, but rather an adulterant!

Acute lethal poisoning in humans is described in several cases, where the intended use of saffron was the induction of abortion. The target organ in acute poisoning is the kidneys. Post mortem histological analyses after lethal doses of the drug generally demonstrated inflammation and congestion of the kidneys, and blood in the urinary tracts and the bladder. A typical and rather well documented severe poisoning of a pregnant woman with abortion, skin reactions and circulatory failure was described after the ingestion of 5 g of „saffron“ in a cup of milk, combined with an oestrogen preparation.

The older literature describes a yellow colouring of the facial skin as an effect of chronic saffron intake in a dose of 1 g/day. Supposedly this effect was used by simulants to create the impression of an icterus. The same effect was supposedly also observed in newborn babies of mothers with a high saffron consumption.

In contrast to these indications saffron was found to have a very low or even non-existent toxicity in *in vivo* studies in animals.

Statements regarding mutagenicity are at best heterogeneous. Saffron was not found mutagenous in the AMES-test in Salmonella typhimurium strain TA98, however, it could not prevent mutagenicity induced by BP. On stimulation by 2AA, safranal was found to be co-mutagenous. However, the same researcher had indicated saffron and its extract fraction as non-toxic, non-mutagenous, and non-co-mutagenous.

Based on the possible use against retinoic acid sensitive tumours, crocetin was tested on teratogenous effects. Crocetin was less teratogenous than retinoic acid in the model of frog embryos.

One case of an anaphylactic reaction to saffron was reported.

The oral allergenicity of saffron is very low. In one single report an IgE mediated reaction was correlated with saffron ingestion. In view of the quantities of saffron consumed world-wide, allergic reactions to ingested saffron can be expected to occur extremely rarely.

On analysis of the data of 589 prick tests on allergies against various spices, coriander, caraway, fennel and celery were responsible for 32 % of positive tests in children and 23 % in adults. In contrast, allergies against saffron were obviously very rare and were only observed in single cases.

The allergic potential of saffron flowers was examined by means of prick and RAST-tests. Three out of 50 saffron workers had a positive reaction to saffron pollen. One of them had a positive bronchial provocation test on asthma, two a rhinoconjunctivitis. In a population of 237 patients with allergies 10 were shown positive on saffron in the skin test and on IgE determination. Cross-reactions were demonstrated for *Lolium*, *Sansola* and *Olea*-species.

Dosage

Typically 0.5-1.0 g of saffron powder per day.

2 x 15mg **Saffron'*Extr*** extract (2% safranal) per day for mood-stabilizing effects.