SAFFRON

Crocus sativus L.

Family

Iridaceae, the iris family. It is a close relative of freesias and gladioli.[1]

Parts Used

Stigma, usually joined at the base to a short style, rarely used plant parts.

Description

The saffron crocus is a perennial, stemless plant that grows from a rounded bulb (or corm). Each bulb produces one to seven flowers with a honey like smell. The blue violet, lily shaped flowers appear in autumn and erect grass-like leaves emerge just before, with or after the flowers. They grow 15cm to 20cm in height. The saffron spice is the stigma of the flowers (the red filaments, or style, that form the female reproductive parts). The pistil includes the top stigma as well as a long style that contains the ovary of the plant. At harvest the whole flower is removed from the plant then the stigma and style are separated from the flower and dried. Saffron is generally traded as whole filaments so the consumer can see they are purchasing pure saffron. The saffron crocus is thought to have originated in south west Asia or the Mediterranean region. It is a sterile flowering plant so it does not produce seed, and therefore its spread throughout the world has been dependent on human activity and the trade and transport of the corms. The finer details of the origins of the saffron crocus are somewhat disputed but generally it is believed that selections were made from the wild species, *Crocus cartwrightianus*, for unusually long stigmas and through this process,

a sterile mutant form now known as *Crocus sativus* has emerged.[2,3]

Traditional Use

Even in the luxurious world of spices saffron stands out. It is highly valued in different cuisines for its distinctive colour, exceptional taste and unique aroma. It holds the salubrious title of the world's most expensive spice with its market price reaching EUR20,000 (approximately AUD30,000) per kilogram. Consequently it is also the target of frequent fraud, adulteration and mislabelling practices. In late 2019 a fake saffron crime ring was uncovered in the United Kingdom which sparked an international investigation. In 2010 Spain exported 190,000 kilograms of saffron, worth 50 million USD (70 million AUD), but the country's total production amounted to only 1500 kilos. At the time a local farmers' union reported that up to 90 per cent of Spanish exports were fraudulent. The industry has tried to crack down on these fake and mislabelled products but the problem still persists and the market for fake saffron is closing many real saffron farmers down.[4,5]

Saffron can be found on the market in the form of entire dried stigmas (the raw material used by The Herbal Extract Company) or as a finely ground powder. Powdered saffron has the ability to be adulterated by other products, especially turmeric *(Curcuma longa)* and by the yellow stamen (male reproductive parts) of the saffron flower. Gardenia *(Gardenia jasminoides)*, butterfly bush tree *(Buddleja officinalis)*, safflower *(Carthamus tinctorius)* and calendula *(Calendula officinalis)* are among the most frequently used adulterants in saffron. For the detection of plant adulterants in saffron there are several chromatographic methods, nuclear magnetic resonance spectroscopy and modern genetic fingerprinting techniques. A new and sophisticated saffron adulteration method with gardenia was recently discovered in the European saffron market but a 2017 analytical methodology has been developed for the detection of the adulteration of saffron samples with gardenia through the determination of geniposide as an adulteration marker.[6,7]

Also known as red gold, or the golden spice, the high price is a result of the high manual labour required for its cultivation, harvesting and handling. It is painstakingly harvested by hand from the light purple, autumn flowers of the small, low growing crocus. It can take 40 hours of hard manual labour to produce just one kilogram of high quality saffron. Each flower yields only three small reddish threadlike stigmas (the female organ). Approximately 150,000 to 250,000 flowers must be carefully picked one by one in order to produce one kilogram of the spice. Or about 15 to 20 flowers are needed to produce 100 milligrams of saffron filaments, which, if high quality, is the quantity required to colour and flavour a dish for four to eight people. Iran is the world's largest producer of saffron and accounts for more than 90 per cent of world production. It is also an important export from Kashmir in India. The production of saffron in Australia is a small but growing industry. Statistics from the last 10 years indicate that there were 80 saffron producers in Australia, producing about 10 kilograms annually.[8,9,10,11]

From time immemorial saffron has also been considered a medicinal plant because it possesses therapeutic properties. This is illustrated in frescoes found on the island of Santorini, dating back to 1627 BC, where it is possible to observe an offering of some type of crocus stigmas (saffron or *Crocus cartwrightianus*) being made to the goddess Thera. Though saffron is best known for its use in traditional Persian medicine it was also used by the ancient Greeks and Egyptians, as well as in the Ayurvedic tradition of India. Its traditional medical indications were many and included cramps, asthma, menstrual conditions, liver disease and pain. In Ayurveda, saffron is said to support the tonic action of other herbs (such as shatavari) and when used as a spice promotes assimilation of food into deeper tissues. The origin of the word saffron is the French term *safran*, which was derived from the Latin word *safranum*, and comes from the Arabic word "*za'faran*" that means "yellow" reflecting the high concentration of carotenoid pigments present in the stigmas. In seventh century BC it appeared in an Assyrian botanical dictionary in which it was indicated for breathing difficulties, painful urination, menstrual disorders and "diseases of the brain", the last two uses corresponding to some of the best researched modern applications. Culpeper also noted that saffron "quickens the brains". Saffron was

included in the Catalogues of Medicinal Plants and in the European Pharmacopoeia, from the 16th until the 20th centuries, being part of a great number of compounded formulas. During the Middle Ages (5th to 15th Centuries) it was used by midwives in deliveries for the sedative and antispasmodic action. It has also been used to treat eye diseases, heal wounds, fractures and joint pain and for many other uses, leading to Pliny the Elder describing it as a kind of panacea in his Naturae Historiarum XXXVII.[12]

Constituents

Crocin and crocetin, carotenoid oxidation products (mainly safranal and the bitter glucoside picrocrocin), zeaxanthin, lycopene, carotene and vitamins particularly riboflavin (vit B2) and thiamine (vit B1). The intense red colour comes from an extraordinarily high content of carotenoid molecules, mainly the crocins. When saffron is consumed the crocins release the carotenoid crocetin into the bloodstream. The odour and flavour comes from the carotenoid oxidation products, mainly safranal for the aroma and the bitter comes from the glucoside picrocrocin.[13,14]

Actions

Nervine tonic, antidepressant, anxiolytic, adaptogen (TCM), neuroprotective, cognitive enhancer, sedative, antioxidant, anti-inflammatory, anticarcinogenic, antinociceptive (inhibits the sensation of pain), analgesic, anticonvulsant, expectorant, emmenagogue, aphrodisiac, cardiotonic, hypotensive, antispasmodic, diaphoretic, hypoglycaemic, hypolipidaemic.

Pharmacological Activity

Throughout the past three decades increased scientific attention has been given to examining saffron's use as a potential therapeutic or preventive agent for a number of health conditions including cancer, cardiovascular disease and depression. Saffron has been shown to improve numerous health related physiological and psychological outcomes. A recent systematic review examined the current state of scientific evidence from randomised controlled trials regarding the efficacy of saffron on psychological and behavioural outcomes. Findings from initial clinical trials suggest that saffron can improve the symptoms and effects of depression, premenstrual syndrome, sexual dysfunction and infertility, and excessive snacking behaviours. A selection of these trials is below.[15]

Alzheihmer's Disease Activity

Preliminary trials of saffron's impact on brain function and the management of Alzheimer's disease are promising. In a 2020 systematic review of randomised controlled trials saffron was shown to be equally effective to common symptomatic drugs for mild cognitive impairment and Alzheimer's disease and resulted in no difference in the incidence of side effects when compared with placebo or drugs.[16]

In a double-blind, randomised, controlled phase 2 study saffron was found to be as effective as donepezil, one of the most recently approved cholinesterase inhibitors which are the leading class of Alzheimer's drugs. The results indicate that patients with mild to moderate Alzheimer's disease receiving saffron experienced statistically significant benefits in cognition after 22 weeks treatment. The dose of saffron was 15mg a day for four weeks increased to 15mg twice a day for 18 weeks. Forty-seven people completed the study (24 in the saffron group and 23 in the donepezil group). Scores on the Alzheimer's Disease Assessment Scale-Cognitive Subscale improved by 3.96 points in the saffron group and by 3.77 points in the donepezil group. Scores on the Clinical Dementia Rating Scale-Sums of Boxes improved by 0.77 points in the saffron group and by 0.83 points in the donepezil group. While there was no statistical difference between saffron and donepezil saffron did have an advantage in adverse events, vomiting occurred significantly more frequently in the donepezil group.[17]

Similarly the use of saffron in 46 patients with mild-to-moderate Alzheimer's disease for 16 weeks improved cognitive function. In this randomised, double-blind, placebo-controlled study each person was given either a placebo or 15mg of saffron extract twice a day for 16 weeks. The researchers said that saffron's mechanism in benefiting Alzheimer's disease may be the inhibition of aggregation and deposition of amyloid beta plaque in the brain.[18]

Depression and Insomnia Activity

Saffron is also nicknamed the "sunshine spice" not just due to its distinct colour but because it may also help brighten the mood. Saffron was used in traditional Persian medicine for treating depression and depression is the condition for which saffron has the strongest scientific support. The initial evidence was provided by two small, double-blind studies. The first was a six week, randomised, double-blind, placebo-controlled trial of 35 people with mild to moderate depression who were given either a placebo or 30mg of saffron. The saffron was not standardised. At the end of the six-week study the saffron group had a significantly greater improvement on the Hamilton Rating Scale for Depression.[19]

Results of a 28 day, parallel group, double-blind, randomised controlled trial published earlier this year (2020) suggest saffron intake was associated with improvements in sleep quality in adults with self-reported sleep complaints. Fifty five healthy adults with self-reported sleep problems were randomised to receive either saffron extract (14mg twice daily) or a placebo. Previous research in 2019 by the scientists showed saffron (14mg twice daily) was an effective add on to pharmaceutical antidepressants in patients experiencing mild to moderate depression. Many of the people in the study reported improvements in their sleep. This was an eight week, randomised, double-blind, placebo-controlled study.[20,21]

There are more than half a dozen clinical trials conducted evaluating the efficacy of saffron in mild-to-moderate depression where saffron was shown to be more effective than placebo at alleviating depression and just as active as conventional drugs, including fluoxetine (Prozac - a selective serotonin reuptake inhibitor (SSRI) which can cause sexual dysfunction), where saffron has also been shown to improve fluoxetine-induced sexual dysfunction in both men and women. In other words it can improve the side effects of these conventional treatments. It appears to be safe to add to conventional antidepressant drugs especially SSRIs.[22,23,24]

A randomised study conducted in Iran for two months found that saffron alleviated five major symptoms of withdrawal in patients undergoing maintenance treatment for opioid addiction. The symptoms included diarrhea, rhinorrhoea, myalgia, temptation, and loss of appetite. Forty-four men of addiction treatment centres, aged from 21 to 67 years, participated. The test group was treated with methadone syrup and "self-made" saffron capsules (30mg), and the control group received methadone syrup and placebo capsules. All participants were stable, had received a fixed dose of methadone for several months, and did not have any mental or physical symptoms. The saffron and placebo capsules were dispensed by the researcher once a week for eight weeks in the clinic at the time of the weekly dose of methadone. The methadone dose was decreased by 5mg per week. Patients had 24-hour access to medical help by phone, and symptoms were recorded at the clinic each week.[25]

A 2017 randomised, double-blind study found a significant decrease in negative mood and symptoms related to stress and anxiety compared to placebo in adults reporting low mood, when treated with concentrated extract of saffron (28mg/day) for four weeks. A lower dose of extract (22mg/day) was not effective. The beneficial effects were more prominent for depression (by reducing negative affect rather than increasing positive affect) and stress.[26]

The same extract was tested in a randomised, double-blind, placebo-controlled trial in teenagers aged 12 to 16 who were suffering from mild to moderate depression or anxiety. Patients were given tablets containing placebo or saffron (14mg twice a day) for eight weeks. Saffron was associated with greater improvements in depression, separation anxiety and social phobia.[27]

Saffron (50mg twice a day), taken for 12 weeks, significantly improved symptoms in patients with mild to moderate mixed anxiety and depression in a recent double-blind, randomised, placebo-controlled trial.[28]

In a double-blind, randomised and placebo-controlled trial conducted on 60 new mothers saffron (15mg twice a day), taken for eight weeks, reduced the severity of depression in those with postpartum, mild to moderate depression.[29]

Reproductive Health Activity

In traditional medicine saffron has been used as a facilitator of difficult delivery, was useful in treating uterus pain and for regulating the menstrual cycle.

A recent study showed that the use of saffron can shorten the delivery process. In this study 30 women were randomly divided into two groups who took saffron capsules (250mg) and placebo capsules as positive group and control group, respectively. The results showed that administration of saffron capsule at the beginning of the active phase of labour (one capsule every two hours for maximum three capsules) could shorten the active phase of labour time in saffron consumer group.[30]

Saffron stigma (30mg/day of extract) over two menstrual cycles significantly relieved symptoms of premenstrual syndrome (PMS) in a double-blind, placebo-controlled clinical trial. In this study they used saffron stigma prepared as follows: 120g of dried and milled petal was extracted with 1800mL ethanol (80%) by percolation procedure in three steps, then the ethanolic extract was dried by evaporation in temperature between 35 to 40°C. Each capsule had dried extract of saffron (15mg), lactose (filler), magnesium stearate (lubricant) and sodium starch glycolate (disintegrant).[31]

Saffron was significantly better than placebo for postmenopausal women who were experiencing hot flushes and mild to moderate depression. Fifty six women completed the study. They randomly received either saffron (15mg twice a day) or placebo for six weeks.[32]

Eye Health Activity

As would be expected, given its high levels of carotenoids, saffron is showing promise in eye health especially for the retina. The influence of saffron on retinal health was first clinically investigated by researchers from Italy and Australia in a double-blind trial that was reported in December 2010. Daily intake (20mg) of saffron for 90 days was associated with a significant improvement in retinal function in 25 patients with age related macular degeneration.[33]

Saffron supplementation (20mg per day for three months) modestly improved visual function in participants with age related macular degeneration a 2019 randomised clinical trial in 100 people found.[34]

A recent double-blind placebo-controlled randomised trial found that daily supplementation with 30mg of saffron for six months may result in a midterm, significant improvement in retinal function in 60 patients with age related macular degeneration.[35]

Glaucoma is caused by increased pressure within the eye, known as intraocular pressure. Saffron extract seemed to exert an ocular hypotensive effect (to reduce the intraocular pressure of the eye) in primary open angle glaucoma. This effect became evident after three weeks of therapy. The researchers said the role of oxidative damage in the development of glaucoma makes antioxidants such as saffron an attractive target for potential clinical use. Thirty-four clinically stable glaucoma patients receiving treatment with timolol and dorzolamide eye drops were enrolled in this prospective, comparative, randomised interventional pilot study. Seventeen people received saffron (30mg per day) for one month as an adjunct to timolol and dorzolamide.[36]

Cardiovascular, Type 2 Diabetes, Weight Loss and Exercise Activity

A recent review article summarised different studies regarding the beneficial properties of saffron in different components of metabolic syndrome including high blood pressure, high fat, high blood glucose and obesity. The results of the most relevant animal and human studies showed the potential use of this plant in metabolic syndrome risk factors especially diabetes mellitus. The researchers concluded that saffron has therapeutic potential particularly in cardiovascular disease.[37]

Saffron supplementation (100mg per day) in type 2 diabetes patients had beneficial effects on blood pressure as it decreased systolic blood pressure after 12 weeks. This 2019 placebo-controlled, randomised clinical trial was performed on 80 type 2 diabetes patients. Subjects were randomly assigned to either saffron (40 people) or placebo (40 people) groups.[38]

Saffron could prevent metabolic syndrome and prevent increases in blood glucose. The aim of a recent randomised triple-blind placebo-controlled study was to assess whether saffron prevents olanzapine induced metabolic syndrome and insulin resistance in patients with schizophrenia. Twenty two patients diagnosed with schizophrenia who were on olanzapine (an antipsychotic drug)

treatment (5 to 20mg daily) were randomly allocated to receive a 30mg capsule of saffron daily for 12 weeks. There was a significant difference in fasting blood sugar in the saffron group. In addition, saffron could effectively prevent reaching the criteria of metabolic syndrome as early as week six.[39]

Saffron seems to be a valuable discovery to reduce food craving and snacking. Based on preclinical and clinical studies reporting positive antianxiety and antidepressant effects for saffron, a team of French scientists wondered if the herb might balance mood and reduce snacking and the desire to eat, making it a suitable supplement for people undertaking weight loss programs. In a randomised clinical trial in 60 women saffron treatment (176.5mg per day) resulted in a significantly greater body weight reduction than placebo over eight weeks. But the main result was a striking reduction in weekly snacking events with saffron (reduced from 6.1 to 2.9) compared to the placebo group (reduced from 6.3 to 4.5). The researchers concluded that a combination of an adequate diet with saffron might help people engaged in a weight loss program in achieving their objective.[40]

In patients with metabolic syndrome 100mg daily of saffron for 12 weeks produced improvement in some indices related to risk factors for cardiovascular disease (i.e. heat shock proteins).[41]

Recent evidence has suggested the use of saffron as an antidiabetic drug. The hypoglycaemic and hypolipidaemic effects of saffron were reported in several animal studies involving experimental diabetes and its complications such as diabetic nephropathy and encephalopathy.[42]

Delayed onset muscle soreness (DOMS) is the pain and discomfort that may be felt for a few days after strenuous exercise. It is experienced as stiffness, tenderness, and pain during physical activity. DOMS is problematic for people in training because, aside from the discomfort, it can limit exercise and training. In a randomised, double-blind, placebo-controlled trial, 39 sedentary men were given a placebo, 300mg of saffron, or 75mg of the nonsteroidal anti-inflammatory drug indomethacin for 10 days, starting one week before exercise and continuing for three days. The placebo group experienced severe pain for three days after the exercise, but pain in the saffron group was 11.2 times lower than baseline scores after 24 hours. Pain in the indomethacin group took three days to disappear, but the saffron group had no pain after 48 hours. The researchers concluded that saffron can be used to prevent DOMS and alleviate DOMS symptoms.[43]

Asthma Activity

Several studies, including a 2019 double-blind, randomised placebo-controlled trial, have reported the effects of saffron on asthmatic patients suggesting that saffron seems to be an effective and safe option (in eight weeks supplementation) to improve clinical symptoms of patients with allergic asthma. Saffron (two 50mg oral capsules daily) improved the frequency of clinical symptoms of the patients (i.e. frequency of the shortness of breath during the day and night time, use of salbutamol spray, waking up due to asthma symptoms and activity limitation) in comparison to the placebo. Besides, asthma severity decreased almost significantly in the saffron group. It was also found that saffron, in comparison with the placebo, significantly reduced the systolic and diastolic blood pressure, triglycerides and low density lipoprotein cholesterol.[44]

Urinary System Activity

Herbalists and traditional healers in the West Bank regions of Palestine use saffron as one of the principal herbs for bed wetting.[45]

Immune and Cancer Activity

Saffron has demonstrated antitumour and cancer preventive activities *in vivo* and *in vitro* but the exact mechanism of the anticancer effect is not clear. Researchers have suggested that the anticancer activity of saffron and its compounds is related to antioxidant properties of carotenoids.[46]

Saffron may have short term immunomodulating effects. The results of a randomised clinical trial suggest that the sub chronic daily use of 100mg of saffron has temporary immunomodulatory activities without any adverse effects. In the study 45 healthy men took saffron for six weeks.[47]

Indications

- Low mood, mild to moderate depression, anxiety, insomnia, cognitive disorders, to improve brain function, Alzheimer's disease, Parkinson's disease
- Respiratory issues including cough, asthma
- Liver disease
- To support normal menstruation and for menstruation problems such as dysmenorrhoea, PMS, chronic uterine haemorrhage
- Pain, spasms, osteoarthritis, traditionally used for seizures
- Colic, bedwetting
- Cardiovascular disorders, diabetes, weight loss, obesity, metabolic syndrome
- To support healthy retinal function, eye health, macular degeneration
- Fevers
- Potential role in the treatment of cancer

Energetics

Sweet, neutral.

Use in Pregnancy

Saffron has been used as a spice and food colouring agent for centuries and is likely to be safe when consumed in the usual dietary doses. Whether high dose saffron is safe in pregnancy remains to be confirmed.

Contraindications

Saffron should be used under professional supervision in the treatment of any mental health condition to promote safety.

Drug Interactions

Possible additive effects with hypotensive, hypoglycaemic, anticoagulant and antiplatelet medications.[49]

Administration and Dosage

Liquid Extract:	1:20
Alcohol:	50%
Weekly Dosage:[50]	5 to 25mL

(1mL is equivalent to 50mg of the dry herb)

Saffron is so highly concentrated in carotenoids that effective clinical doses are not high, helping to keep the cost down. The common effective doses in clinical trials is 30 to 50mg per day. The trials in age related macular degeneration used just 20mg of dried stigma per day. Most of the other trials used 30mg per day of a concentrated extract, probably corresponding to around 180mg per day of stigma.[53,54]

References

1. Saffron. [Internet] AgriFutures Australia is the trading name for Rural Industries Research & Development Corporation (RIRDC), a statutory authority of the Federal Government established by the Primary Industries Research and Development Act 1989. [updated 24 May 2017]. Available from https://www.agrifutures.com.au/farm-diversity/saffron/
2. Saffron. [Internet] AgriFutures Australia is the trading name for Rural Industries Research & Development Corporation (RIRDC), a statutory authority of the Federal Government established by the Primary Industries Research and Development Act 1989. [updated 24 May 2017]. Available from https://www.agrifutures.com.au/farm-diversity/saffron/
3. Moshiri M, Vahabzadeh M, Hosseinzadeh H. Clinical Applications of Saffron (Crocus sativus) and its Constituents: A Review. Drug Research. 2015 Jun;65(6):287-295. DOI: 10.1055/s-0034-1375681.
4. Soffritti G, Busconi M, Sánchez RA, Thiercelin JM, Polissiou M, Roldán M, et al. Genetic and Epigenetic Approaches for the Possible Detection of Adulteration and Auto-Adulteration in Saffron (Crocus sativus L.) Spice. Molecules. 2016 Mar 11;21(3):343. doi: 10.3390/molecules21030343.
5. Floyd C. Real saffron can cost you over $10,000 per kilo. Here's what makes it so expensive. [Internet] Business Insider Australia. [updated June 28 2020]. Available from https://www.businessinsider.com.au/why-real-saffron-is-so-expensive-2020-6?r=US&IR=T
6. Soffritti G, Busconi M, Sánchez RA, Thiercelin JM, Polissiou M, Roldán M, et al. Genetic and Epigenetic Approaches for the Possible Detection of Adulteration and Auto-Adulteration in Saffron (Crocus sativus L.) Spice. Molecules. 2016 Mar 11;21(3):343. doi: 10.3390/molecules21030343.
7. Guijarro-Díez M, Castro-Puyana M, Luis Crego A, Luisa Marina M. Detection of saffron adulteration with gardenia extracts through the determination of geniposide by liquid chromatography–mass spectrometry. Journal of Food Composition and Analysis. 2017 Jan;55:30–37.
8. Kyriakoudi A, Ordoudi SA, Roldán-Medina M, Tsimidou MZ. Saffron, A Functional Spice. Austin J Nutri Food Sci. 2015;3(1): 1059. ISSN: 2381-8980.
9. Moore JC, Spink J, Lipp M. Development and application of a database of food ingredient fraud and economically motivated adulteration from 1980 to 2010. J Food Sci. 2012 Apr;77(4):R118-26. doi: 10.1111/j.1750-3841.2012.02657.x. Epub 2012 Apr 4.
10. Soffritti G, Busconi M, Sánchez RA, Thiercelin JM, Polissiou M, Roldán M, et al. Genetic and Epigenetic Approaches for the Possible Detection of Adulteration and Auto-Adulteration in Saffron (Crocus sativus L.) Spice. Molecules. 2016 Mar 11;21(3):343. doi: 10.3390/molecules21030343.
11. Saffron. [Internet] AgriFutures Australia is the trading name for Rural Industries Research & Development Corporation (RIRDC), a statutory authority of the Federal Government established by the Primary Industries Research and Development Act 1989. [updated 24 May 2017]. Available from https://www.agrifutures.com.au/farm-diversity/saffron/
12. José Bagur M, Alonso Salinas GL, Jiménez-Monreal AM, et al. Saffron: An Old Medicinal Plant and a Potential Novel Functional Food. Molecules. 2017;23(1):30. Published 2017 Dec 23. doi:10.3390/molecules23010030
13. Gohari AR, Saeidnia S, Mahmoodabadi MK. An overview on saffron, phytochemicals, and medicinal properties. Pharmacogn Rev. 2013 Jan;7(13):61-6. doi: 10.4103/0973-7847.112850.
14. Mollazadeh H, Emami SA, Hosseinzadeh H. Razi's Al-Hawi and saffron (Crocus sativus): a review. Iran J Basic Med Sci. 2015;18:1153–1166.
15. Hausenblas HA, Heekin K, Mutchie HL, Anton S. A systematic review of randomized controlled trials examining the effectiveness of saffron (Crocus sativus L.) on psychological and behavioral outcomes. J Integr Med. 2015;13(4):231-240. doi:10.1016/S2095-4964(15)60176-5
16. Avgerinos KI, Vrysis C, Chaitidis N, Kolotsiou K, Myserlis PG, Kapogiannis D. Effects of saffron (Crocus sativus L.) on cognitive function. A systematic review of RCTs. Neurol Sci. 2020;41(10):2747-2754. doi:10.1007/s10072-020-04427-0
17. Akhondzadeh S, Shafiee Sabet M, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, et al. A 22-week, multicenter, randomized, double-blind controlled trial of Crocus sativus in the treatment of mild-to-moderate Alzheimer's disease. Psychopharmacology (Berl). 2010 Jan;207(4):637-43. doi: 10.1007/s00213-009-1706-1. Epub 2009 Oct 20.
18. Akhondzadeh S, Sabet MS, Harirchian MH, Togha M, Cheraghmakani H, Razeghi S, et al. Saffron in the treatment of patients with mild to moderate Alzheimer's disease: a 16-week, randomized and placebo-controlled trial. J Clin Pharm Ther. 2010 Oct;35(5):581-8. doi: 10.1111/j.1365-2710.2009.01133.x.
19. Akhondzadeh S, Tahmacebi-Pour N, Noorbala AA, et al. Crocus sativus L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial. Phytother Res. 2005;19(2):148-151. doi:10.1002/ptr.1647
20. Lopresti AL, Smith SJ, Metse AP, Drummond PD. Effects of saffron on sleep quality in healthy adults with self-reported poor sleep: a randomized, double-blind, placebo-controlled trial. J Clin Sleep Med. 2020;16(6):937–947.
21. Lopresti AL, Smith SJ, Hood SD, Drummond PD. Efficacy of a standardised saffron extract (affron®) as an add-on to antidepressant medication for the treatment of persistent depressive symptoms in adults: A randomised, double-blind, placebo-controlled study. J Psychopharmacol. 2019;33(11):1415-1427. doi:10.1177/0269881119867703
22. Bone K. Saffron: An Impressive Range of Health Benefits from this Age-old Spice. Available from http://nutritionandhealing.com/2013/05/22/saffron-health-benefits/
23. Noorbala AA, Akhondzadeh S, Tahmacebi-Pour N, Jamshidi AH. Hydro-alcoholic extract of Crocus sativus L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. J Ethnopharmacol. 2005;97(2):281-284. doi:10.1016/j.jep.2004.11.004
24. Moosavi S M, Ahmadi M, Amini M, Vazirzadeh B. The Effects of 40 and 80 mg Hydro- alcoholic Extract of Crocus Sativus in the Treatment of Mild to Moderate Depression. J Mazandaran Univ Med Sci. 2014; 24 (113) :48-53 URL: http://jmums.mazums.ac.ir/article-1-3745-en.html
25. Shahi MN, Asadi A, Talab EB, Shahi MN. The Impact of Saffron on Symptoms of Withdrawal Syndrome in Patients Undergoing Maintenance Treatment for Opioid Addiction in Sabzevar Parish in 2017. Advances in Medicine. 2017, Article ID 1079132, 5 pages. https://doi.org/10.1155/2017/1079132
26. Kell G, Rao A, Beccaria G, Clayton P, Inarejos-García AM, Prodanov M. affron® a novel saffron extract (Crocus sativus L.) improves mood in healthy adults over 4 weeks in a double-blind, parallel, randomized, placebo-controlled clinical trial. Complement Ther Med. 2017;33:58-64.
27. Lopresti AL, Drummond PD, Inarejos-García AM, Prodanov M. affron®, a standardised extract from saffron (Crocus sativus L.) for the treatment of youth anxiety and depressive symptoms: A randomised, double-blind, placebo-controlled study. J Affect Disord. 2018;232:349-357.
28. Mazidi M, Shemshian M, Mousavi SH, et al. A double-blind, randomized and placebo-controlled trial of Saffron (Crocus sativus L.) in the treatment of anxiety and depression. J Complement Integr Med. 2016;13(2):195-199. doi:10.1515/jcim-2015-0043

29. Tabeshpour J, Sobhani F, Sadjadi SA, et al. A double-blind, randomized, placebo-controlled trial of saffron stigma (Crocus sativus L.) in mothers suffering from mild-to-moderate postpartum depression. Phytomedicine. 2017;36:145-152. doi:10.1016/j.phymed.2017.10.005
30. Mollazadeh H, Emami SA, Hosseinzadeh H. Razi's Al-Hawi and saffron (Crocus sativus): a review. Iran J Basic Med Sci. 2015;18:1153–1166.
31. Agha-Hosseini M, Kashani L, Aleyaseen A, Ghoreishi A, Rahmanpour H, Zarrinara AR, et al. Crocus sativus L. (saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. BJOG. 2008 Mar;115(4):515-9. doi: 10.1111/j.1471-0528.2007.01652.x.
32. Kashani L, Esalatmanesh S, Eftekhari F, et al. Efficacy of Crocus sativus (saffron) in treatment of major depressive disorder associated with post-menopausal hot flashes: a double-blind, randomized, placebo-controlled trial. Arch Gynecol Obstet. 2018;297(3):717-724.
33. Falsini B, Piccardi M, Minnella A, Savastano C, Capoluongo E, Fadda A, et al. Influence of saffron supplementation on retinal flicker sensitivity in early age-related macular degeneration. Invest Ophthalmol Vis Sci. 2010 Dec;51(12):6118-24. doi: 10.1167/iovs.09-4995. Epub 2010 Aug 4.
34. Broadhead GK, Grigg JR, McCluskey P, Hong T, Schlub TE, Chang AA. Saffron therapy for the treatment of mild/moderate age-related macular degeneration: a randomised clinical trial. Graefes Arch Clin Exp Ophthalmol. 2019;257(1):31-40. doi:10.1007/s00417-018-4163-x
35. Lashay A, Sadough G, Ashrafi E, Lashay M, Movassat M, Akhondzadeh S. Short-term Outcomes of Saffron Supplementation in Patients with Age-related Macular Degeneration: A Double-blind, Placebo-controlled, Randomized Trial. Med Hypothesis Discov Innov Ophthalmol. 2016;5(1):32-38.
36. Jabbarpoor Bonyadi MH, Yazdani S, Saadat S. The ocular hypotensive effect of saffron extract in primary open angle glaucoma: a pilot study. BMC Complement Altern Med. 2014;14:399. Published 2014 Oct 15. doi:10.1186/1472-6882-14-399
37. Razavi BM, Hosseinzadeh H. Saffron: a promising natural medicine in the treatment of metabolic syndrome. J Sci Food Agric. 2017;97(6):1679-1685. doi:10.1002/jsfa.8134
38. Ebrahimi F, Aryaeian N, Pahlavani N, et al. The effect of saffron (Crocus sativus L.) supplementation on blood pressure, and renal and liver function in patients with type 2 diabetes mellitus: A double-blinded, randomized clinical trial. Avicenna J Phytomed. 2019;9(4):322-333.
39. Fadai F, Mousavi B, Ashtari Z, et al. Saffron aqueous extract prevents metabolic syndrome in patients with schizophrenia on olanzapine treatment: a randomized triple blind placebo controlled study. Pharmacopsychiatry. 2014;47(4-5):156-161. doi:10.1055/s-0034-1382001
40. Gout B, Bourges C, Paineau-Dubreuil S. Satiereal, a Crocus sativus L extract, reduces snacking and increases satiety in a randomized placebo-controlled study of mildly overweight, healthy women. Nutr Res. 2010 May;30(5):305-13. doi: 10.1016/j.nutres.2010.04.008.
41. Shemshian M, Mousavi SH, Norouzy A, et al. Saffron in metabolic syndrome: its effects on antibody titers to heat-shock proteins 27, 60, 65 and 70. J Complement Integr Med. 2014;11(1):43-49. Published 2014 Feb 6. doi:10.1515/jcim-2013-0047
42. Konstantopoulos P, Doulamis IP, Tzani A, Korou ML, Agapitos E, Vlachos IS, et al. Metabolic effects of Crocus sativus and protective action against non-alcoholic fatty liver disease in diabetic rats. Biomed Rep. 2017 May;6(5):513-518. doi: 10.3892/br.2017.884. Epub 2017 Apr 5.
43. Meamarbashi A, Rajabi A. Preventive effects of 10-day supplementation with saffron and indomethacin on the delayed-onset muscle soreness. Clin J Sport Med. 2015;25(2):105-112. doi:10.1097/JSM.0000000000000113
44. Zilaee M, Hosseini SA, Jafarirad S, et al. An evaluation of the effects of saffron supplementation on the asthma clinical symptoms and asthma severity in patients with mild and moderate persistent allergic asthma: a double-blind, randomized placebo-controlled trial. Respir Res. 2019;20(1):39. Published 2019 Feb 22. doi:10.1186/s12931-019-0998-x
45. Jaradat NA, Zaid AN, Al-Ramahi R, Alqub MA, Hussein F, Hamdan Z, et al. Ethnopharmacological survey of medicinal plants practiced by traditional healers and herbalists for treatment of some urological diseases in the West Bank/Palestine. BMC Complement Altern Med. 2017 May 8;17(1):255. doi: 10.1186/s12906-017-1758-4.
46. Samarghandian S, Borji A. Anticarcinogenic effect of saffron (Crocus sativus L.) and its ingredients. Pharmacognosy Res. 2014 Apr;6(2):99-107. doi: 10.4103/0974-8490.128963.
47. Kianbakht S, Ghazavi A. Immunomodulatory effects of saffron: a randomized double-blind placebo-controlled clinical trial. Phytother Res. 2011;25(12):1801-1805. doi:10.1002/ptr.3484
48. Moshiri M, Vahabzadeh M, Hosseinzadeh H. Clinical Applications of Saffron (Crocus sativus) and its Constituents: A Review. Drug Research. 2015 Jun;65(6):287-295. DOI: 10.1055/s-0034-1375681.
49. Natural Medicines (US). Saffron [Internet]. Somerville (MA): Therapeutic Research Center; 2020 [updated 2019 Sep 16; cited 2020 Sep 3]. Available from https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=857
50. Natural Medicines (US). Saffron [Internet]. Somerville (MA): Therapeutic Research Center; 2020 [updated 2019 Sep 16; cited 2020 Sep 3]. Available from https://naturalmedicines.therapeuticresearch.com/databases/food,-herbs-supplements/professional.aspx?productid=857
51. Kyriakoudi A, Ordoudi SA, Roldán-Medina M, Tsimidou MZ. Saffron, A Functional Spice. Austin J Nutri Food Sci. 2015;3(1): 1059. ISSN: 2381-8980.
52. Bone K. Saffron: An Impressive Range of Health Benefits from this Age-old Spice. Available from http://nutritionandhealing.com/2013/05/22/saffron-health-benefits/