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Clinical Applications of Saffron (Crocus *sativus*) and its Constituents: A literature review

Hosien Shahdadi[1], Farzaneh Barati*[2], Raziyeh Sadat Bahador[3] and Abdulsamad Eteghadi[4]

[1]*Department of Nursing, School of Nursing and Midwifery, Zabol University of Medical Sciences, Zabol, Iran*
[2]*Msc in Nursing Education, Department in Nursing, Neyshabur University of medical sciences, Iran*
[3]*Instructor, MS in Nursing, School of Nursing and Midwifery, Jiroft University of Medical Science, Jiroft, Iran*
[4]*Msc Student, Anatomy Department, Medicine School, Zahedan University of Medical Science, Zahedan, Iran*

ABSTRACT

In this review, we introduce the traditional uses of saffron and its pharmacological activities from recent scientific studies. Modern pharmacological findings on saffron are compared with those mentioned in Avicenna's monograph. A computerized search of published articles was performed using MEDLINE, Scopus and Web of Science databases as well as local references. The search terms used were saffron, Crocus sativus, crocin, crocetin, safranal, picrocrocin, Avicenna and 'Ibn Sina'. Avicenna described various uses of saffron, including its use as an antidepressant, hypnotic, anti-inflammatory, and others. Most of these effects have been studied in modern pharmacology and are well documented. The pharmacological data on saffron and its constituents, including crocin, crocetin and safranal, are similar to those found in Avicenna's monograph. This review indicates that the evaluation of plants based on ethnobotanical information and ancient books may be a valuable approach to finding new biological activities and compounds

Key words: Clinical Applications; Saffron, literature Review

INTRODUCTION

Crocus sativus L (C. sativus), commonly known as saffron, is a small perennial plant belonging to the family of Iridaceas. Description. The domesticated saffron crocus, Crocus sativus, is an autumn-flowering perennial plant unknown in the wild. Its progenitors are possibly the eastern Mediterranean autumn-flowering Crocus cartwrightianus, which is also known as "wild saffron"and originated in Greece.The saffron crocus probably resulted when C. cartwrightianus was subjected to extensive artificial selection by growers seeking longer stigmata. C. thomasii and C. pallasii are other possible sources(1)

SCIENTIFIC CLASSIFICATION
Kingdom : Plantae
Division : Magnoliophyta
Class : Liliopsida
Order : Asparagales
Family : Iridaceae
Genus : Crocus
Species : *C. sativus(2)*

It is a sterile triploid form, which means that three homologous sets of chromosomes compose each specimen's genetic complement; C. sativus bears eight chromosomal bodies per set, making for 24 in total Being sterile, the purple flowers of C. sativus fail to produce viable seeds; reproduction hinges on human assistance: clusters of corms, underground, bulb-like, starch-storing organs, must be dug up, divided, and replanted. A corm survives for one season, producing via this vegetative division up to ten "cormlets" that can grow into new plants in the next season. The compact corms are small, brown globules that can measure as large as 5 cm (2.0 in) in diameter, have a flat base, and are shrouded in a dense mat of parallel fibres; this coat is referred to as the "corm tunic". Corms also bear vertical fibres, thin and net-like, that grow up to 5 cm above the plant's neck(3)

Cultivation

The saffron crocus, unknown in the wild, probably descends from Crocus cartwrightianus, which originated in Crete; C. thomasii and C. pallasii are other possible precursors.The saffron crocus is a triploid that is "self-incompatible" and male sterile; it undergoes aberrant meiosis and is hence incapable of independent sexual reproduction—all propagation is by vegetative multiplication via manual "divide-and-set" of a starter clone or by interspecific hybridisation. If C. sativus is a mutant form of C. cartwrightianus, then it may have emerged via plant breeding, which would have selected for elongated stigmata, in late Bronze Age Crete.(4)

Crocus sativus thrives in the Mediterranean maquis, an ecotype superficially resembling the North American chaparral, and similar climates where hot and dry summer breezes sweep semi-arid lands. It can nonetheless survive cold winters, tolerating frosts as low as −10 °C (14 °F) and short periods of snow cover. Irrigation is required if grown outside of moist environments such as Kashmir, where annual rainfall averages 1,000–1,500 mm (39–59 in); saffron-growing regions in Greece (500 mm or 20 in annually) and Spain (400 mm or 16 in) are far drier than the main cultivating Iranian regions. What makes this possible is the timing of the local wet seasons; generous spring rains and drier summers are optimal. Rain immediately preceding flowering boosts saffron yields; rainy or cold weather during flowering promotes disease and reduces yields. Persistently damp and hot conditions harm the crops,(5) and rabbits, rats, and birds cause damage by digging up corms. Nematodes, leaf rusts, and corm rot pose other threats. Yet Bacillus subtilis inoculation may provide some benefit to growers by speeding corm growth and increasing stigma biomass yield(6).

CHEMISTRY

Saffron contains more than 150 volatile and aroma-yielding compounds. It also has many nonvolatile active components, many of which are carotenoids, including zeaxanthin, lycopene, and various α- and β-carotenes. However, saffron's golden yellow-orange colour is primarily the result of α-crocin. This crocin is trans-crocetin di-(β-D-gentiobiosyl) ester; it bears the systematic (IUPAC) name 8,8-diapo-8,8-carotenoic acid. This means that the crocin underlying saffron's aroma is a digentiobiose ester of the carotenoid crocetin. Crocins themselves are a series of hydrophilic carotenoids that are either monoglycosyl or diglycosyl polyene esters of crocetin.(7) Crocetin is a conjugated polyene dicarboxylic acid that is hydrophobic, and thus oil-soluble. When crocetin is esterified with two water-soluble gentiobioses, which are sugars, a product results that is itself water-soluble. The resultant α-crocin is a carotenoid pigment that may comprise more than 10% of dry saffron's mass. The two esterified gentiobioses make α-crocin ideal for colouring water-based and non-fatty foods such as rice dishes(8).

When saffron is dried after its harvest, the heat, combined with enzymatic action, splits picrocrocin to yield D–glucose and a free safranal molecule. Safranal, a volatile oil, gives saffron much of its distinctive aroma. Safranal is less bitter than picrocrocin and may comprise up to 70% of dry saffron's volatile fraction in some samples. A second element underlying saffron's aroma is 2-hydroxy-4,4,6-trimethyl-2,5-cyclohexadien-1-one, which produces a scent described as saffron, dried hay-like.(9) Chemists find this is the most powerful contributor to saffron's fragrance, despite its presence in a lesser quantity than safranal.Dry saffron is highly sensitive to fluctuating pH levels, and rapidly breaks down chemically in the presence of light and oxidising agents. It must, therefore, be stored away in air-tight containers to minimise contact with atmospheric oxygen. Saffron is somewhat more resistant to heat(10).

Grades and ISO 3632 categories

Saffron is not all of the same quality and strength. Strength is related to several factors including the amount of style picked along with the red stigma. Age of the saffron is also a factor. More style included means the saffron is less strong gram for gram, because the colour and flavour are concentrated in the red stigmata. Saffron from Iran, Spain and Kashmir is classified into various grades according to the relative amounts of red stigma and yellow styles it contains. Grades of Iranian saffron are: "sargol" (red stigma tips only, strongest grade), "pushal" or "pushali" (red

stigmata plus some yellow style, lower strength), "bunch" saffron (red stigmata plus large amount of yellow style, presented in a tiny bundle like a miniature wheatsheaf) and "konge" (yellow style only, claimed to have aroma but with very little, if any, colouring potential). Grades of Spanish saffron are "coupé" (the strongest grade, like Iranian sargol), "mancha" (like Iranian pushal), and in order of further decreasing strength "rio", "standard" and "sierra" saffron. The word "mancha" in the Spanish classification can have two meanings: a general grade of saffron or a very high quality Spanish-grown saffron from a specific geographical origin. Real Spanish-grown La Mancha saffron has PDO protected status and this is displayed on the product packaging. Spanish growers fought hard for Protected Status because they felt that imports of Iranian saffron re-packaged in Spain and sold as "Spanish Mancha saffron" were undermining the genuine La Mancha brand(11, 12).

Countries producing less saffron do not have specialised words for different grades and may only produce one grade. Artisan producers in Europe and New Zealand have offset their higher labour charges for saffron harvesting by targeting quality, only offering extremely high grade saffron(13).

In addition to descriptions based on how the saffron is picked, saffron may be categorised under the international standard ISO 3632 after laboratory measurement of crocin (responsible for saffron's colour), picrocrocin (taste), and safranal (fragrance or aroma) content. However, often there is no clear grading information on the product packaging and little of the saffron readily available in UK is labelled with ISO category. This lack of information makes it hard for customers to make informed choices when comparing prices and buying saffron(14).

Under ISO 3632, determination of non-stigma content ("floral waste content") and other extraneous matter such as inorganic material ("ash") are also key. Grading standards are set by the International Organization for Standardization, a federation of national standards bodies. ISO 3632 deals exclusively with saffron and establishes three categories: III (poorest quality), II, and I (finest quality). Formerly there was also category IV, which was below category III. Samples are assigned categories by gauging the spice's crocin and picrocrocin content, revealed by measurements of specific spectrophotometric absorbance. Safranal is treated slightly differently and rather than there being threshold levels for each category, samples must give a reading of 20–50 for all categories(15).

PHARMACOLOGICAL ACTIONS

Antihypertensive activity

Fatehi and others investigated the effects of C. sativus petals' extract on blood pressure in anesthetized rats and also on responses of the isolated rat vas deferens and guinea -pig ileum induced by electrical field stimulation (EFS). Aqueous and ethanol extracts of C. sativus petals' reduced the blood pressure in a dose-dependent manner. Administration of 50 mg/g of aqueous extract changed the blood pressure from 133.5 ± 3.9 to 117 ± 2.1 (mmHg). This reduction could either be due to the effect of the C. sativus petals' extracts on the heart itself/total peripheral resistance, or both. The effect of extracts on peripheral resistance seems to be more important.(16)In the rat isolated vas deferens, contractile responses to EFS were decreased by the petals' extracts. Contractions of the vas deferens to EFS are mediated by a combination of noradrenaline and ATP released as cotransmitters from sympathetic nerves(17). The ethanol extract induced greater changes in EFS in the rat isolated vas deferens and guinea- pig ileum than the aqueous extract(18)

Anticonvulsant activity

The anticonvulsant activities of C. sativus stigma constituents, safranal and crocin, were evaluated in mice using pentylenetetrazole (PTZ)-induced convulsions in mice. Safranal (0.15 and 0.35 ml/kg body weight, i.p.) reduced the seizure duration, delayed the onset of tonic convulsions, and protected mice from death. Crocin (22 mg/kg, i.p.) did not show anticonvulsant activity(19)

Antitussive activity

The antitussive activity of C. sativus stigma and petal extracts and its components, safranal and crocin, was evaluated using the nebolized solution of citric acid 20% in guinea pigs. The ethanolic extract of C. sativus (100-800 mg/kg) and safranal (0.25-0.75 ml/kg) reduced the number of cough. The ethanolic and aqueous extracts of petal and crocin did not show antitussive activity(20)

Antigenototoxic and cytotoxic effects of saffron

The antimutagenic, comutagenic, and cytotoxic effects were assessed using the Ames/Salmonella test system, two well-known mutagen (BP, 2AA), the in vitro colony-forming assay, and four different cultured human normal

(CCD-18LU) and malignant (Hela,a-204 and Hepg2) cells. When only using the TA98 strain in the Ames/Salmonella test system, saffron showed nonmutagenic, as well as non-antimutagenic activity against BP-induced mutagenicity and demonstrated a dose-dependent co-mutagenic effect on 2-AA-induced antimutagenicity. The saffron component responsible for this unusual co-mutagenic effect was safranal. In the in vitro colony-forming test system, saffron displayed a dose-dependent inhibitory effect only against human malignant cells. All isolated carotenoid ingredients of saffron demonstrated cytotoxic activity against in vitro tumor cells. Saffron crocin derivatives possessed a stronger inhibitory effect on tumor cell colony formation. Overall, these results suggest that saffron itself, as well as its carotenoid components, might be used as potential cancer chemopreventive agents(21)

Effect on sexual behavior

The aphrodisiac activities of C. sativus stigma aqueous extract and its constituents, safranal and crocin, were evaluated in male rats. The aqueous extract (80, 160, and 320 mg/kg body wt.), crocin (100, 200, and 400 mg/kg body wt.), safranal (0.1, 0.2, and 0.4 ml/kg), sildenafil (60 mg/kg body wt., as a positive control), and saline were administered intraperitoneally to male rats. Mounting frequency (MF), mount latency (ML), intromission latency (IL), and ejaculation latency (EL) were the factors evaluated during the sexual behavior study. Crocin, at all doses, and the extract, especially at doses 160 and 320 mg/kg body wt., increased MF, IF, and EF behaviors and reduced EL, IL, and ML parameters. Safranal did not show aphrodisiac effects. This study exhibited an aphrodisiac activity of saffron aqueous extract and its constituent crocin(18, 22)

Effect on learning behavior and long-term potentiation

The saffron extract and two of its main ingredients, crocin and crocetin, improved memory and learning skills in ethanol-induced learning behavior impairments in mice and rats. Oral administration of saffron may be useful in the treatment of neurodegenerative disorders and related memory impairment(19)

Effects on ocular blood flow and retinal function

Crocin analogs isolated from saffron significantly increased the blood flow in the retina and choroid as well as facilitated retinal function recovery and it could be used to treat ischemic retinopathy and/or age-related macular degeneration.(23)

Antinociceptive and anti-inflammatory effects

Saffron stigma and petal extracts exhibited antinociceptive effects in chemically induced pain test as well as acute and/or chronic anti-inflammatory activity, and these effects might be due to the presence of flavonoids, tannins, anthocyanins, alkaloids, and saponins(24)

USES

Saffron in therapeutics

The Ebers papyrus (ca 1550 B.C.) mentions saffron as an ingredient in a cure for kidney problems. It was recommended as an addition to each meal as “a cheering cardiac medicament,” but with a warning that excessive quantities acted as an appetite depressant,(25)although a reasonable amount would stimulate appetite and ease headaches and hangovers. In the recent times, it is being used as a remedy for catarrhal infections, for melancholia, to treat liver enlargement, as a nerve sedative,(5) as a carminative, diaphoretic, and emmenagogue. Its extensive use as an abortifacient decreased following reports of fatalities; death has occurred after ingestion of 1.5 g. Saffron has been discovered to be easily the richest known source of riboflavin, with about 100 γ/g. Saffron would be likely to offset the decreased diffusivity of oxygen caused by elevated plasma protein and cholesterol level, reduced the severity of atherosclerosis. In addition, serum cholesterol levels were reduced by half. (26)The addition of crocetin to an appropriate nutrient fermentation broth was found to increase the yield of antibiotics and other products. Modern pharmacological studies have demonstrated that saffron extract or its constituents have antidepressant, anti-inflammatory, anti-tumor effects, radical-scavenging, learning and memory improving properties. Saffron extract also has chemoprotective properties and protects from genotoxin-induced oxidative stress in mice. Anticonvulsant effects have been reported in both PTZ and maximal electroshock (MES) models in mice(27).

Saffron as dye

Dyes and colored garments (principal pigment of saffron is α-crocin, a water-soluble carotenoid). Saffron has been used as a histological stain, i.e., as a dye for connective tissue (28)

Saffron as perfume
A pleasantly odoriferous compound, safranal, develops during the drying process, probably by enzymatic or thermal dissociation of the bitter compound, picrocrocin.(29)

Saffron in food
It performs the functions of a spice, adding its faint, delicate aroma, pleasing flavor, and magnificent yellow color to enhance palatability(30)

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