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Review Article

Unani perspective of Saffron (*Crocus sativus* Linn.) beyond a spice

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Abstract

Background: Saffron is a significant medicinal herb that has a lot of potential for use in the development of new drugs. Since ancient times, saffron (*Crocus sativus* L.) has been associated with various health benefits in various parts of the world. Some of these applications have been overlooked over time. However, interest in naturally occurring active compounds has rekindled interest in saffron's past applications and the best applications for saffron today can be aided by knowing its various historical uses. It was prized as a culinary spice as well as a perfume, color, and medicinal herb. It was used medicinally in many different cultures to treat a wide range of ailments, from genitourinary to eye problems. In many countries, it was also used as an antidepressant and tonic substance.

Objective: The purpose of this review is to provide an overview of the traditional and modern uses of *Crocus sativus*, with particular attention to its chemical makeup, pharmacological characteristics, and ethnobotanical description.

Methodology: Scientific databases and publications about the chemical profile, biological activity, and historical use of saffron were included in the literature search.

Results: Saffron is *bitter, acrid, fragrant, stimulant, tonic, stomachic, aphrodisiac, anodyne*, antispasmodic, emmenagogue, diuretic, laxative, galactagogue, and helpful in treating bronchitis, vomiting, fever, melancholia, hepatomegaly, etc. it is widely used in alternative medicine, such as the Unani System of Medicine, Ayurveda, and Traditional Chinese Medicine. Saffron has been the subject of numerous phytochemical and biochemical studies due to its extensive use in traditional medical systems. These studies have revealed that saffron contains a number of constituents, including crocetin, safranal, and crocins, the latter of which is primarily responsible for pharmacological actions.

Keywords; saffron, medicinal herb, unani medicine, crocetin, safranal, emmenagogue.

Introduction:

C. Sativus (varn, kesar) belongs to Iridacae family and two more plants that belong to the family are Iris (cultivated for Gorgeous flowers) and Sipura poludosa (a garden plant), while as the saffron is cultivated extensively in Kashmir, the deep red colored dried stigmas for commercial purposes.[1] The dried stigmas and upper part or top of the styles of *Crocus sativus* L. is called the saffron. The world's most expensive, most precious spice and genuine saffron is worth its weight in gold. Out of almost 85 species belonging to the Crocus genus, saffron is the most pleasing and arousing spice.[2] Because of its sterility, this plant can only be multiplied by growing corms. Before creating and developing corm harvesting, handling, sizing, and sowing equipment, it is necessary to consider the physical characteristics of saffron corms.[3] *Zafran* is made up of the stigmas from *Crocus sativus* flowers, a tiny corm-sheathed bulbous herb that grows to a height of 15 to 25 cm. The leaves have a curved back, channeled margins, and a narrow, linear shape. The purple to violet-colored flowers can be found alone or in clusters. There are three stigmas: dilated upward, folded in different ways, jagged, or enucleated.[4] The term *"Zafran"* refers to the deep red internal stigma. When the stigma of *Zafran* is dissolved in water, a rich yellow color results. *Zafran* is a brain and cardiotonic, detergent, and resolvent drug. It is native to the Levant in Asia Minor and, on small scales, cultivated in parts of Kashmir and Quetta. *Zafran* is used to treat a few inflammatory conditions that affect different body organs, such as metritis and hepatitis. It functions as an emmenagogue and diuretic. [7] Saffron is mainly cultivated in Iran (estimated to account for about 90% of world production), followed by India, Spain, Morocco, Greece, and Italy (Babaei et al., 2014; Shokrpour, 2019).[8] The stigmas of *Zafran* are dark red, pleasant in odour, and have a bitter taste.[9]It is mentioned in a Persian book written by Aman-ullah Khan, known as Ganj Badawrad, that *Zafran* has so many varieties. One variety is known as "Joezi," likely to be from Spain; the other variety is called 'Magash' (milky).[10] The root of *Zafran* is like *Zaravand Mudaharaj* (*Aristolochia Rotunda),* and the flowers are like those of *Suranjan.* The best variety of *Zafran* is from Kashmir, followed by Asfahan (Iran), Mazandran (Iran), and then other parts of the world.[11]Saffron is mentioned in sacred and divine books like the Holy Quran and the Holy Bible.[2]

Materials and Methods:

To gather all pertinent data on saffron (*Crocus sativus* L.), a literature search was conducted using publicly accessible electronic databases, such as PubMed, Scopus, Google Scholar, Science Direct, Research Gate, and other online resources and from the literature available in the central library of NIUM Bengaluru. The key words applied for the search were Zafran, Saffron, Crocus sativus, and Kesar.

Historical background:

A degree of uncertainty surrounds the origin of the English word "saffron". It might stem from the 12th-century Old French term safran, which comes from the Latin word safranum, from the Arabic (زَعْفَرَان), za'farān, which comes from the Persian word zarparan meaning "gold strung" (implying either the golden stamens of the flower or the golden color it creates when used as flavor) [12] Regarding the origin of saffron, several theories are put forth. Documented evidence suggests that it originated in Iran, most likely in the Alvand Mountains and Zagross. The term "Gouishi" or "Kerkomise" refers to wild saffron that resembles domesticated species. For example, the corms, leaves, stamen, and style of Crocus are similar to those of Gouishi. However, gouishi has no economic value due to its short style and weak odour. The earliest records of the use of saffron go back to the "Achaemenian" dynasty, an ancient Persian state, [13] it appears that the two main producing and exporting nations are Iran and Spain, with saffron also grown in Kashmir and Afghanistan. It is thought that Zoroastrians, who arrived in India when Arabs entered Iran, brought saffron to Kashmir (Abrishami, 1997). There is disagreement among scientists about the nativity of the saffron plant; some think it originated in the Orient, while others think it originated in Greece (Raina et al., 1996; Sampathu, 2000).[14] Historical accounts indicate that the first known fully developed civilization originated in the Fertile Crescent, located between the Tigris and the Euphrates, and that saffron was used there as a medicine. It was customary in Mesopotamia to prescribe and use medications while uttering magic words and making symbolic gestures because they felt that doing so would endow the drugs with healing properties. Like other countries at the time, their materia medica included items from the vegetable, animal, and mineral kingdoms, such as fig, onion, garlic, saffron, mustard, myrrh, cypress, salt, milk, meet, and animal fat.[15]

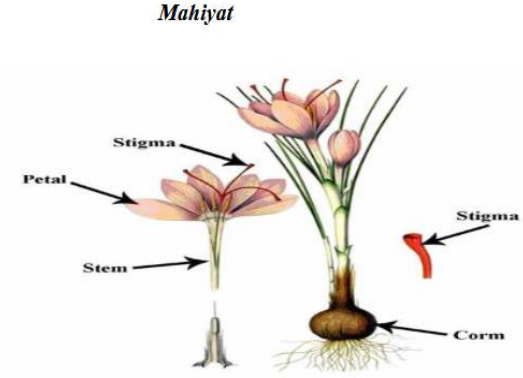
Plantation and cultivation:

The most appropriate time for planting the saffron corm is the second fortnight of August. [2] But the plantation is done at different times in different regions according to the weather conditions of the region, such as in Spain, where it is planted in the middle of May and early June, and in Kashmir, from the middle of July to the end of August. [14] The *Zafran* is planted on a high level of land where water may not accumulate. [10] The soil for hoeing of saffron corms requires well preparation, and it is important to raise the beds to avoid water lodging, with a convenient slope all around drains of convenient depth and width, giving it the shape of a good flower bed. The small plots were raised and surrounded by drains 22 cm. wide and 15 cm. deep, laid out in well-pulverized soil, to make them quite suitable for transplantation. The corms are planted at a depth of 8–10 cm. and 15–20 cm apart in straight rows, with usually a distance of 18 cm between the rows. Before the expected time of flowering, the soil is pulverized a few times so that the flowers can come out easily without any damage. The corms, once established, continue to live for 10–15 years, with new corms being produced annually and the old ones rooting away. [16] Persistently damp and hot conditions harm the crop, and rabbits, rats, and birds cause damage by digging up corms. Nematodes, leaf rusts, and corm rot pose other threats. [17]

Harvesting:

Saffron crocus is a delicate-looking lavender plant that produces stigmas. When harvested and dried, these stigmas create saffron. It is one of the costliest spices in the world; therefore, its cultivation has great economic significance wherever it takes place. [18] Approximately one hundred and fifty flowers together yield one gramme (1GM) of dry saffron threads; to produce 12g of dried saffron, 1kg of flowers are needed. An average of 30 mg of fresh or 7 mg of dried saffron can be obtained from one freshly picked flower. [19]

Physical properties:



Different parts of crocus plant; Medan et.al [2]

The plant sprouts 5–11 white, non-photosynthetic leaves known as cataphylls. These membrane-like structures cover and protect 5 to 11 true leaves, which are thin, straight, and blade-like green foliage, 1–3 mm in diameter. They either expand after the flowers have opened ("hysteranthous") or do so simultaneously with their blooming ("synanthous"). If the plants are irrigated earlier in the growing season, then the latter *C. sativus* cataphylls may grow prior to blooming.[19] It contains stigmas with a bright red colour and styles with an orange-yellow color. At first, the flowers come out of the soil, and after that, leaves arise from the corum, which is about 10–15 cm long and green in colour, and the corum (root) is like that of an onion. [20] Fragrant flowers, about 1-4 from each corm, dark lilac or violet to purple, flower from November to December. The root stock is a sheeted corm, which is 3–5 cm; it has no stem, and the leaves are radical, narrowly linear, and channeled with curved margins. Flowers are about 25 mm across, solitary or clustered, and narrowly sessile. It contains a funnel-shaped calyx, a slender tube, and six lobes in two series of petal colors like light violet, reddish-purple, or mauve colored.[16]

Names in different languages:

Arabic; *Zafran*, kurkum [9, 21]

Persian; kemass [21] **Bengali;** Jafran [9]

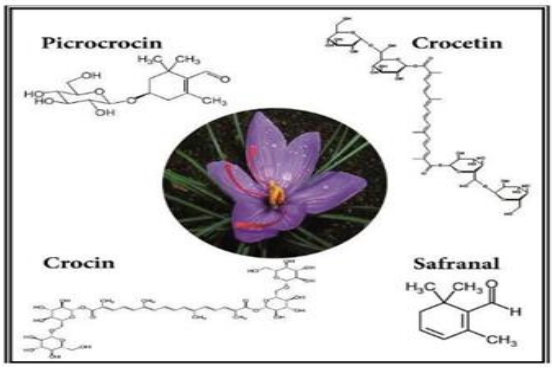
Hindi; Kesar, kumkum, kankoon [21]

Kannad; Kunkumakesari, **Marathi;** Kesra, **Oriya;** Kesaro, **Sanskrit;** Keshara, **Tamil;** Kungumapu, **Telugu;** Kunkumnpave[22] **Kashmiri;** Kong, **Urdu;** Zafran[4, 23] **English;** Safran[7,22] **Polish**; Szafran, **Portuguese**; Acafrao, **Russian**; –Schafran, **Spanish**; Azafran, **Swedish**; Saffron and **Turkish;** Zafar[16]

Taxonomical classification:

Botanical name; *Crocus sativus* L.[24] **Family**; Iridaceae [2, 4] **Kingdom;** Plantae **Division:** Magnoliophyta, **Class:** Liliopsida **Order:** Asparagales, **Genus:** Crocus **Species:** Sativus [25]

Chemical constituents;



Diagrammatic representation of chemical constituents of saffron [26]

Saffron contains glucosides of crocin, crocetin, picrocrocin, and essential oils. [23]

Three crystalline coloring substances: [1] a-Crocetin (C24H28O5 M. P. 272-273°) constitutes 0.7% of saffron; [2] B-crocetin (C25H30 O5 M. P. 205 206) constitutes 0-7% of saffron; and [3] Y-crocetin (C26H3205 M. P. 202-203") constitutes 0.3%. A volatile fatty oil, 8 to 3.4%, Crocin, a glucoside soluble slightly in water, freely in alkaline solution and alcohol, and forming 65% of polycrotic, which is the coloring matter, picrocrocin (bitter principle), wax, proetids, fixed essential oil (1.37%),, mucilage, sugar, ash (5%) and moisture (12%) [6] also contains carotenes like B, R, and lycopene. [24] Four isolectins have been isolated from the bulbs. The molecular weights of these lectins are approx. 48 kDa. The tepal extract contains the flavanol aglycones, myricetin, quercetin, and kaempferol, the anthocyanidins, delphinidin and petunidin, and the flavonoids, astragalin, helichrysoside, kaempferol-3-O-ß-D-glu-copyranosyl-(l→2)-b-D-6 acetyl glucopyranoside, and kaempferol-3-0-B-D- glucopyranosyl-(1→2)-ß-D glucopyranoside. The pollen contains the glycosides, crosatosides A and B, and kaempferol-3-O-ß-D-glucopyranosyl (1→2), -ß-D-glucopyranoside. The lectins agglutinated yeast cells but did not agglutinate animal erythrocytes. The stigma showed remarkable inhibitory effects on blood coagulation due to the presence of a platelet aggregation inhibitor containing adenosine. It prolonged both PT and aPTT and accelerated the in vitro fibrinolytic activity of urokinase and plasmin. The IC50 values of the inhibitor against platelet aggregation induced by ADP and collagen are 7.5 and 0.82 mg/ml, respectively.[27, 28]

In addition to these important chemicals, saffron oil also contains terpene derivatives, pinene, and cineol. Phytochemical studies also indicated that the presence of flavonoids such as rutin, quercetin, luteolin, hesperidin, bioflavonoids, tannins, and anthocyanins in flower petals may be responsible for their antinociceptive, anti-inflammatory, and blood pressure-lowering effects. [29]

Approximate analysis of components of saffron:

Component	%age	Component	%age
Water soluble components	53.0	Lipids	12.0
Gums	10.0	Non- volatile oils	6.0
Pentosans	8.0	Volatile oils	1.0
Pectin's	6.0	Proteins	12.0
Starch	6.0	Inorganic matter(ash)	6.0
α- crocin	2.0	HCL soluble ash	0.5
Carotenoids	1.0	Crude fiber	5.0
Water	10.0		

Table 1 [30, 2]

Part used: Stigmas only and sometimes with styles [4, 6, 24, 31]

Mizaj/ Temperament: Hot 2 and dry1[10, 20, 32] Hot 3, Dry1[6]

Actions (*Afa'al*):

Saffron (Crocus sativus L.) is mostly used as medicine to promote health and fight disease from old times. In countries like India and other Asian countries, saffron is used very frequently in different alternative systems of medicine, including the Unani System of Medicine, Ayurveda, and Traditional Chinese Medicine, as it is considered bitter, acrid, fragrant, stimulant, tonic, stomachic, aphrodisiac, anodyne, antispasmodic, emmenagogue, diuretic, laxative, galactagogue, and useful in bronchitis, cephalgia, vomiting, fever, melancholia, hepatomegaly, etc. [2] It acts as a tonic for internal viscera like the kidney, bladder, and liver; a cardio tonic; a nervine tonic; and a resolvent for uterine swellings. [20] As reported by Jalinoos (Gallen), saffron is *kabiz* (constipative), *Munzij* (coctive), and anti-putrefactive (*da'afe ufoonat*). [11, 21] Used in fevers, melancholia, and hepatomegaly, [23] *Zof-e-Reham, Zof-e-Meda, Qulanj* (colic), *Ehtibas-e-Tams,* antispasmodic, emmenagogue[4, 6, 11, 33] and is a good medicine for uterine pain. [34] Aqueous and ethanol extracts of *C. sativus* petals have been found to reduce blood pressure in a dose-dependent manner. The placebo-controlled clinical trials conducted to evaluate the efficacy of saffron in mild-to-moderate depression reported it to be more effective and at least equivalent to therapeutic doses of imipramine and fluoxetine. The stigmas and petals of saffron extract have shown anti-nociceptive and anti-inflammatory activities. Besides the traditional uses of saffron from ancient times, new pharmacological studies have shown many other properties as preventive and curative in so many ailments of the cardiovascular, central nervous, respiratory, gastrointestinal, and urogenital systems. [29] In European medicine, it is used chiefly as a colouring and flavoring agent. It is given to cage birds when they are molting or have other sick conditions, with a few threads being infused in the water that they drink. [35] Unani scholars have taken privilege in describing the medicinal properties of saffron from ancient times and defining its effectiveness. This precious and valuable drug has been described as having the following properties in addition to the above-mentioned *afa'al* (functions): *Majalli Basr* (correcting eye sight), *Muhalil* (resolvent), [11,36] *Muharrik-e-bah* (sexual stimulant), [4,36,37] *Mufarreh* (exhilarant), *Mufatteh* (deobstruent),[4,6,38] *Muqawwie aalaat-e tanaffus* (a tonic for the respiratory system) is used in dry cough, whooping cough, bronchitis, [37] *Muqawwie meda* (stomachic), [4] *Mullayin* (apaarient), *Muqawwie dimag* (brain tonic), [2] *Mugharri* (agglutinant), [36] *Musakin* (sedative), [4] Skin fairness [2,36]

Uses: Saffron is included in other medicines, as atonement, which are used as remedies for hepatic and uterine ailments (hepatitis, metritis). It is placed in the urethra for urinary retention and in the pessary as an emmenagogue, and for this purpose, it can be taken with hot milk. [7] It is chiefly used as a flavoring and colouring agent and by the laity (rich) in the form of tea as a stimulant, antispasmodic, diaphoretic (in measles), and emmenagogue. [31] One mithqal (3.642 gams) of saffron taken with any advisable liquid eases difficult labor, and ten (10) carats (2 gm) taken daily resolve splenomegaly. If saffron is used with honey, it removes renal calculus and is useful in uterine and rectal pain with other medicines. [11] If saffron is mixed with fat, wax, and twice the quantity of olive oil, it resolves the hardness of the uterus and cervical constriction. The ointment of saffron and *Farfiyon* (Resin Spurge, *Eudicots resinifera*) is beneficial for arthralgia and gout. [11] It is mentioned in Al Hawi that saffron oil, wax, egg yolk, and twice the quantity of olive oil as a compound formulation acts as analgesic and heal uterine ulcers. [34] Saffron extract and extracts of *Nigella sativa, Ixora javanica*, and *Saraca asoca* are

the principle constituents of a preparation used for the treatment of cancer in the Ayush system of medicines. Saffron extract showed cytotoxic, anti-mutagenic, and anti-tumor activity in mice. [27] 50mg of saffron dissolved in 100 ml of milk twice daily given to human subjects and the significant decrease in lipoprotein oxidant susceptibility in patients with coronary artery disease describe the potential of saffron as an antioxidant. [38, 39, 40]

Saffron is dissolved in rose water to treat cardiac ailments like cardiac weakness, palpitations, and liver disorders like ascites, jaundice, and liver tonics. In this form, it is also used in organomegalies (visceral enlargements), general weakness, and as an aphrodisiac. It is dissolved in water and instilled in the nose for rhinitis and other acute inflammations. [41]

***Miqdar-e-khurak* (Dosage):**

It is mentioned in different dosages in different texts, but the recommended therapeutic doses are mentioned as 500 mg–1.5 gm,[37] 1.75–3.5 gm,[11] 1–4 gm, and [4] 0.5–1 gm.[41,42] The dose of the drug is from 1 to 3 grains, and the dose of the tincture is ½ to 2 drachms. [35] 1-4 grains (64.79 mg–260 mg),[4]10–15 stigmata/cup water (APA); 0.5–1.5 g day (APA; HHB); saffron (PNC); 0.1–1 g powdered saffron (MAD); 15–16 drops tincture (MAD) [43]

Toxic dose: Severe side effects may result from ingesting 5 g of saffron (LD = 20 g). “Hazards and/or side effects are not known for proper therapeutic dosages." Commission E reports no risks for doses up to 1.5 g; however, 5 g is toxic, 10 g is abortive, and 20 g is lethal. Animal studies indicate that LD50 is 20.7 g/kg in decoction form. [40]

***Mudhir* (Harmful):** It causes weakness in the kidneys, decreased appetite in higher doses, [41, 42] head aches, and disturbances in the stomach. [11] High doses of saffron should be avoided in pregnancy; quantity ≥5 gm can act as a uterine stimulant and abortifacient. [44]

***Musleh* (correctives):** *Anisoon* (*Pimpinella anisum* L.) [9, 41, 42] *Zarishik* (*berberis aristata), shikanjabeen* [9]

***Badal* (Substitute):** *Utraj* (*Citrus medica* L.) [41, 42] *Quest* (*saussurea lappa*) [9, 41]

Murakabaat (Important formulations of saffron in Unani and Ayurveda):

- *Jawarish-e-Jalinoos*, *Dawa-ul-kurkum kabeer wa sagheer* [41]
- *Jawarish-e-mastagi* [42]
- *Majoon-e-Dabeed-ul-Warad, Daw-ul-misk moetadil sada wa jawahar, Mufareh Yaqooti Sada Wa Jawahir*[9,44]
- Kumkumadi Ghrita and Kumkumadi Taila[16]

Evidence based pharmacological activities:

Immunomodulatory effect of *C. sativus* L. The carotenoids in *C. sativus* L. include crocetin, crocin, as well as monoterpene aldehydes, picrocrocin, and safranal, which are the major constituents that improve immune functions. In a clinical trial, it was shown that daily consumption of a 100 mg saffron tablet by 45 healthy volunteers for 06 weeks increased IgG but decreased IgM levels compared to the baseline and placebo groups. The results also showed increased monocyte percentages compared to placebo but decreased basophil percentages and platelet count after 3 weeks. However, after 6 weeks, these altered values were restored to their baseline levels. These results indicate that immunomodulatory activity could be considered for 100 mg/day of saffron without causing any adverse effects. [46]

Anti-inflammatory, antimicrobial activity; The effect of saffron on various inflammatory disorders (i.e., anti-inflammatory effect) was stated in traditional medicine as a dissolvent of swellings. It is also painted on erysipelas (an acute streptococcal infection characterized by deep-red inflammation of the skin and mucous membranes).[47] Recent studies on different disease-producing microorganisms have revealed promising antimicrobial and antibacterial activities. The saffron extract has been utilized on gram-positive bacteria (Staphylococcus aureus and Bacillus subtilis), gram-negative bacteria (Klebsiella pneumonia), and one yeast, Candida albicans. [48] Saffron stigma and petal extracts exhibited antinociceptive effects in chemical pain tests as well as acute and/or chronic anti-inflammatory activity, and these effects might be due to their content of flavonoids, tannins, anthocyanins, alkaloids, and saponins (Hosseinzadeh and Yiounesi, 2002). [38]

Effect of antioxidants from *C. sativus* L. on the cardiovascular system: Recent in vitro and in vivo studies indicate that saffron may have cardio-protective effects through modulation of oxidative stress, calcium channel-blocking effects, and hypotensive and hypolipidemic properties. Atherosclerosis, the most prominent cause of CVDs, is caused by atherogenesis, inflammation in the innermost layer of the vessels that induces pro-inflammatory cytokines and chemokines. In addition, the release of adhesion molecules and oxidative stress are also involved. Heart tissue is vulnerable to oxidative damage because it has a higher oxidative metabolism than other tissues and a lower antioxidant defence than other tissues. Saffron, like certain other medicinal plants, has strong anti-inflammatory and antioxidant qualities that come naturally. Based on preliminary phytochemical evidence, it is suggested that the antioxidant and anti-inflammatory properties of saffron extract are primarily attributed to carotenoids, flavonoids, and anthocyanins, among other constituents. According to Akhondzadeh et al., the antioxidant activity of the stigma of Crocus sativus was higher in methanol and water-methanol (50:50 v/v) extracts than in carrot and tomato extracts. After safranal, the carotenoid components of saffron, crocin, and crocetin demonstrated strong radical-scavenging abilities. The saffron extract's antioxidant capacity is linked to a synergistic effect. [49] Various saffron-derived compounds have demonstrated biological activity that may lessen the severity of numerous cardiovascular diseases. For instance, flavonoids' antioxidant effect, hypocholesterolemic and antidiabetic actions, antiatherosclerotic and vasorelaxant qualities, and other mechanisms can all help to improve cardiovascular health. In a similar vein, the biological activities of the carotenoids found in saffron, including crocin, lutein, and zeaxanthin, may have numerous cardiovascular advantages. [50]

Effect on the digestive system: The medicinal properties of saffron were described by Avicenna a long time ago. He mentioned various biological effects of saffron in the Canon of Medicine, including stomach pain, reduced appetite, gastric hyperacidity, and improved digestion. According to Avicenna's book of the Canon of Medicine, there are various hepatoprotective herbs such as *C. sativus* (saffron), *Pistacia lentiscus* (*mastagi),* and *Cinnamomum* spp. (*darchini*) for the treatment of liver injury from an early age. Among these age-old medicinal plants, it seems that C. sativus has great therapeutic potential for liver disorders and that the utilization of saffron has an impact on the synthesis of serum proteins like albumin by changing the status of liver cell function. [26]

Effect on respiratory system; Saffron has been exclusively used, in traditional medicine, for the treatment of respiratory ailments as bronchodilator and anti-inflammatory agent and

in other inflammatory conditions of the body, which indicates that it could be of therapeutic value in the treatment of lung inflammatory disorders like asthma and other COPD disorders.[51, 27] it eases the respiratory distress by strengthening the respiratory organs.[47]

Saffron as a functional food: Saffron is one of the many foodstuffs that have traditionally been associated with beneficial and even medicinal effects. It has been used for thousands of years as a spice and is notable both for its nutritional goodness and medicinal qualities. There are so many terminologies ascribed to these dietary food products that also have medicinal values, such as functional foods, designer foods, nutraceuticals, and pharma foods. When a legal definition is to be considered, they can only be referred to as new foods, medical foods, dietary supplements, herbs, or medicinal plants, and saffron is one of the most powerful and well-known among these pharmaceutical nutritional foods. [47]

Effect on Hot Flushes: One of the most upsetting experiences for a woman is having a hot flash. Many women seek relief through alternative methods such as lifestyle changes and safe medications like other medical systems, and they feel very comfortable using natural herbal medications. Hormonal and antidepressant conventional medicines have many side effects and can become dependent on long-term use. Till now, so many medicines have been successfully evaluated for this purpose. Among these well-known are evening primrose oil (*Oenothera biennis*), soy products, black cohosh (*Actaea racemose* L.), flax seed oil (*Linum usitatissimum*), St. John's wort (*Hypericum perforatum*), ginseng (*Panax quinquefolius* L.), and saffron (*C. sativus* L.). It has a serotonergic mechanism that is involved in the treatment of depression. It also relieves anxiety and is effective in Alzhemeir's disease without causing any adverse effect on sexual desire, as is generally associated with antidepressants like Fluoxetine, but can prevent such adverse effects. [52]

Effect on the severity of premenstrual syndrome: Aside from its long history of use in medicine to treat a wide range of conditions, including pain, indigestion, decreased appetite, flatulence, anxiety, dysmenorrhea, and sexual weakness, new experimental and clinical trial findings show that saffron is also useful in treating mild to moderate depression. Saffron has an antidepressant effect via a serotonergic mechanism. The mechanism by which crocin demonstrates its antidepressant effects is probably through blocking the reuptake of norepinephrine and dopamine, whereas safranal works by blocking the reuptake of serotonin. For six weeks, taking 20 mg of fluoxetine capsules or 30 mg of saffron capsules twice daily is as effective in treating mild to moderate depression (Noorbala et al.). A comparison of imipramine (100 mg) and saffron (30 mg) given every eight hours Similar outcomes were observed in a six-week study comparing the effects of eight hourly saffron 30 mg capsules with 100 mg imipramine capsules for the treatment of mild to moderate depression (Akhoundzadeh et al.). Another study examined the effects of saffron odour on irregular menstruation, dysmenorrhea, and premenstrual syndrome (PMS). Thirty-five women with a normal sense of smell were exposed to saffron odour for twenty minutes. The results showed a decrease in 17-α estradiol levels, an increase in cortisol levels, and a decrease in the STAI score (State-Trait Anxiety Inventory) in both the luteal and follicular phases. These findings confirm the physiological and psychological effects of saffron odour (Fukui et al.). A comparison of eight-hourly saffron (30 mg) and imipramine (100 mg) on females Agha-Hosseini et al. conducted a clinical trial on 50 women aged 20 to 45 to determine whether saffron could effectively reduce the intensity of PMS. They found that taking 15 mg of saffron twice a day for two menstrual cycles resulted in a 50% reduction in the severity of PMS symptoms in 75% of participants and a 50% reduction in depression symptoms in 60% of participants in the intervention group. on women Agha-Hosseini et al. carried out a clinical trial to find out the effectiveness of saffron in reducing the intensity of PMS in 50 women aged 20–45 and confirmed that 15 mg of saffron twice a day for two menstrual cycles led to a decrease in 50% of the severity of PMS symptoms in 75% of individuals and a decrease in 50% of depression symptoms in 60% of individuals in the intervention group.[53]

Effect on mood and psychological behavior: Depressive symptoms comprising anxiety, stress, and low mood are closely related, and non-pharmacological solutions to improve subclinical mood symptoms and quickness to defeat stress, natural products such as saffron is established with future success after preliminary beneficial effects in major depressive disorders, represent a relevant strategy. Depression is one of the most prevalent psychiatric disorders and has been presumed to involve over 300 million people worldwide, representing about 4.4% of the world's total population. Treatments other than conventional medicines, such as natural products or physical methods like exercise, meditation, etc., to overcome mood disorders are therefore being explored. Among natural products, saffron (the dried stigma of C. sativus) appears to be a promising substance. It is traditionally used in Asian (particularly Persian and Unani) medicine to treat a range of physical ailments, including menstrual disorders, inflammation, and depressive symptoms. A meta-analysis of five clinical trials revealed a treatment effect of saffron compared with placebo and similar antidepressant efficacy when compared with antidepressant medications (fluoxetine, imipramine) at a dose of 30 mg/day for at least 6 weeks in participants with major depressive disorder. The therapeutic effect of extracts of saffron, like Crocin, was identified as an antagonist of the non-selective serotonin receptor agonist mCPP, which is known to induce excessive grooming in rats and exaggerate symptoms in human patients with obsessive-compulsive disorders. [54]

Effects on hyperglycemia and dyslipidemia: The effect of saffron extract in reducing the increased blood sugar levels seems to be influenced by processes including enhancement of glucose uptake by peripheral tissues (Yang et al., 2003), reduction in glucose absorption by the intestine (Youn et al., 2004), (Achrekar et al., 1991), production of endogenous glucose inhibition (Eddouks et al., 2002), and decrease in renal glucose reabsorption (Maghrani et al., 2005) or correction of insulin resistance (Hu et al., 2003) stimulation of βcells of islets of Langerhans to release more insulin (Xi et al., 2007) regeneration of β-cells islets of Langerhans (Elgazar et al., 2013). Hyperglycemia is often associated with increased levels of serum lipid fractions that may lead to major coronary artery disease in most diabetics. Decreased activity of lipolytic hormones is mainly responsible for the elevation of these lipids in adipocyte tissues. Under normal circumstances, insulin activates the enzyme lipoprotein lipase, which hydrolyzes triglycerides. However, insulin deficiency or insulin resistance in diabetic patients leads to hypertriglyceridemia and hypocholesteremia by inactivating lipoprotein lipase (Sharma et al., 2003). Elevated levels of TG, TC, and LDL-C and low circulating levels of HDL are usually associated with DM (Sharma et al., 2003). Many mechanisms for the hypo-lipidemic effects of saffron extract and its constituents have been suggested: (1) modulatory effects on the oxidant-antioxidant system (Xiang et al., 2006); (2) inhibitory effects on pancreatic lipase. It may act by reducing the absorption of fat and cholesterol through inhibiting pancreatic lipase activity (Sheng et al., 2006). [55]

Effect of saffron on menstrual disorders: From ancient times, saffron (*Zafran*) was described in old classical literature as having the properties of being analgesic, antispasmodic, and emmenagogue.

- Used as *Dafa-e Tashanuj* [antispasmodic] [6,31,33,35]
- *Musakin* [sedative] [4]
- *Mudir-e-tams*[Emmenagogue][5,10]
- In Chinese medicine it is used in menstrual disorders [37]
- Used in uterine pain [7, 34]
- It is effective in alleviating premenstrual symptoms [2]
- Menstruation is induced by saffron, which also lessens the associated lumber pain. [18]

Abbreviations:

APA- Ayurvedic professionals association

MAD- Multiascending dose

KDa- Kilodalton

PNC- Perinuclear compartment

Conclusion:

Saffron (*Crocus sativus* L.) has been linked to a number of health advantages in different parts of the world since ancient times. An important medicinal herb with great potential for use in the creation of new medications. Because of its widespread application in conventional medical systems, saffron has been the focus of countless phytochemical and biochemical investigations. These investigations have demonstrated the presence of several constituents in saffron, such as crocetin, safranal, and crocin, the latter of which is principally accountable for the pharmacological effects. Therefore, a thorough evaluation of this priceless herbal remedy for a range of illnesses is required.

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