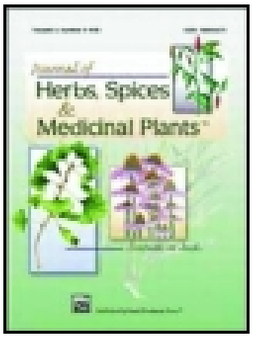

Journal of Herbs, Spices & Medicinal Plants

ISSN: 1049-6475 (Print) 1540-3580 (Online) Journal homepage: http://www.tandfonline.com/loi/whsm20

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To cite this article: Saiful Izwan Abd Razak, Mohd Syahir Anwar Hamzah, Foong Choi Yee, Mohammed Rafiq Abdul Kadir & Nadirul Hasraf Mat Nayan (2017): A Review on Medicinal Properties of Saffron toward Major Diseases, Journal of Herbs, Spices & Medicinal Plants, DOI: 10.1080/10496475.2016.1272522

To link to this article: http://dx.doi.org/10.1080/10496475.2016.1272522

Published online: 17 Feb 2017.

JOURNAL OF HERBS, SPICES & MEDICINAL PLANTS
http://dx.doi.org/10.1080/10496475.2016.1272522

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A Review on Medicinal Properties of Saffron toward Major Diseases

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ABSTRACT
The stigma of *Crocus sativus*, known as saffron, is one of the most expensive spices in the world. The bioactive components in saffron, picrocrocin, crocin, and safranal, have demonstrated a wide range of uses and capabilities in the medical field. This review is focused on the potential therapeutic applications of saffron on diabetes mellitus (DM), antitumor, anticancer, antidepressant, Alzheimer's disease (AD), cardiovascular disease (CVD), erectile dysfunction and antibacterial effects.

ARTICLE HISTORY
Received 16 June 2016

KEYWORDS
Crocus sativus; herbal medicine; diabetes mellitus; cardiovascular disease; antidepressant; cancer; erectile dysfunction; antibacterial

Introduction

Crocus sativus (Iridaceae) (Figure 1) flowers only during autumn and is dormant during summer. Its stigma, named saffron, derived from the Arabic name *azaferan*, is one of the most expensive spices in the world. Physiologically, *C. sativus* has lilac to mauve-colored tepals (51). The stigma is bright red in color and can grow as long as 25–30 mm. It is propagated vegetatively, as the flowers are sterile.

The cultivation of saffron is spread from the eastern Mediterranean region to Europe as well as to Asia. Iran is the main producer of saffron in the world, with an annual production of ~230 tons, accounting for ~93.7% of the world total production in 2005 (51). High or low temperatures of the summer or winter do not affect the plant growth, however, extreme low temperature or extreme humid environment does not promote growth of this plant.

Flowering usually lasts about four or five weeks, and the only way to harvest the crop is by hand picking, which is time-consuming. Each flower has only three stigmas, and to produce 1 kg of saffron spice, about 63 kg of flowers are needed (51). It takes ~14–55 min to pick 1,000 flowers and

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Figure 1. *Crocus sativus* flower and the stigma.

another 100–130 min to remove the stigmas for drying, thus overall the whole process takes about 370–470 hours to produce 1 kg of dried saffron.

With regard to their medicinal usage, many scientific articles have been published documenting antioxidant properties and treatment of cancer and cardiovascular disease. Reviews on these matters also have been given throughout the literatures (7, 11, 27). The antioxidant property is a major contributor that helps to prevent or reduce diseases (35).

Saffron farming

Warm subtropical climate and well-drained sandy soils are the most suitable and preferable for saffron planting. Overly humid soils are not suitable for the plant growth because water is unable to flow easily. Therefore, siliceous, argillaceous-ferruginous, and chalky dry soils are preferred. Best soils for saffron farming are calcium containing soils, because the calcium will help to break down or decompose organic compounds easily. A solid underground corm of the saffron plant is terminated at its adventitious roots. The corm reproduces annually, and the new young corm replaces the dead or older ones. Plowing or preparation of soil for the saffron should be done by hand digging to prevent the corms from damage. The corm production is affected by the planting depth.

Saffron plants only bloom for about 15 d, and the flowers are picked manually every morning before the sun gets too hot, cleaned, and the style and stigmas are separated from the perianth on the same day, as the flower will wilt the next day and the separation of stigmas becomes very difficult. A mechanical saffron flower harvesting system has been developed to harvest the flower without separating the saffron flower from the leaves, which can simplify the mechanical detachment of the flower and thus prevent the fragile stem bends and breaks. This can ensure that a perfect flower can be pick up by the workers (6).

The harvested stigmas are dehydrated and preserved as saffron. Stigmas lose about 80% of their weight during the drying process, and the physical, biochemical, and chemical properties change during this process. A moisture content of <12% is needed to maintain and preserve the quality of product for a longer period (ISO 3632, 29).

There are two dehydration methods that vary in terms of temperature: one is done at room temperature directly under sun or in air-ventilated conditions, and the second method is by drying at higher temperatures using hot air or any other heating source. India, Morocco, and Iran carry out the drying process through the first method, while in India the stigmas are dried under the sun for 3–5 d until the moisture content is reduced to 8–10% (33). In Morocco, the stigmas are spread on a cloth in a very thin layer and dried under the sun for a few hours or in shade for 7–10 d.

In Italy, stigmas are spread on a sieve and placed above live oak-wood charcoal at a distance of ~20 cm above the heat source; during the dehydration process, stigmas are turned to ensure that all the stigmas are dried evenly. When the stigmas do not crumble and still contain a certain amount of elasticity when pressed between the fingers, the dehydration is stopped at ~5–20%. Drying in Greece starts with spreading the fresh stigmas and part of the stamens on shallow-layer trays with a silk cloth on the bottom. During the first hours of the dehydration process, the room temperature is maintained at 20°C and then it is increased to 35–45°C. The relative humidity is maintained at ~50%. Dehydration is stopped when the moisture is reduced to ~10–11%, and this takes about 12 h (44).

The drying process in Spain is called toasting. First, stigmas are spread on a sieve with a silk bottom. Then the sieve is placed over a heating source, which can be a gas cooker, live vine shoot charcoal, or an electric coil. The process is stopped when 85–95% of the moisture has been lost (3).

Brightest color was obtained at higher temperature of 83°C and lower heating times of 28 min. This was due to the more porous sample obtained at high temperature compared to that of the dehydrated sample at room temperature (10). Mild condition (55°C) during the dehydration produced good saffron coloring, and more volatile compounds, mainly safranal, were generated during the dehydration procedure at 55°C (16).

Traditional use of saffron

Saffron has been used in European cuisine since antiquity to color and flavor foods. In addition, it is one of the important and traditional ingredients in German saffron cake, called *Gugelhupf*. Some dairy products also include saffron for flavor and color. Ancient Romans believed that saffron had the ability to prevent hangovers when used for steeping their wine. It also has sedative, antispasmodic, expectorant, as well as aphrodisiac properties.

Higher dosage of saffron may to be toxic, having been used as an abortifacient formerly, and fatal cases have been reported when saffron was used as an abortifacient. Excessive dosage can lead to temporary paralysis. Furthermore, saffron corms have a huge effect on young animals, and it can be used as a narcotic drug when overdosed (39).

Chemical composition of saffron

Saffron is composed of water, nitrogenous matter, sugars, soluble extracts, volatile oil, and fibers. Saffron is rich in vitamins riboflavin (56–138 $\mu g.g^{-1}$) and thiamine (0.7–4 $\mu g.g^{-1}$) (7). The bitter taste of saffron originates from its picrocrocin (β-D-glucosida of hydroxysafranal). The cleavage of carotenoid zeaxanthin will produce picrocrocin and crocin as well as safranal [Figure 2 (47)]. It is a glycoside resulting from the cracking of acid and alkali into a glucose molecule and an aglycon. This aglycon easily undergoes hydrolysis and turns into volatile safranal. The increase in temperature while drying converts the picrocrocin into safranal. Zeaxanthin, reddish in color, is one of the carotenoids found naturally in retina.

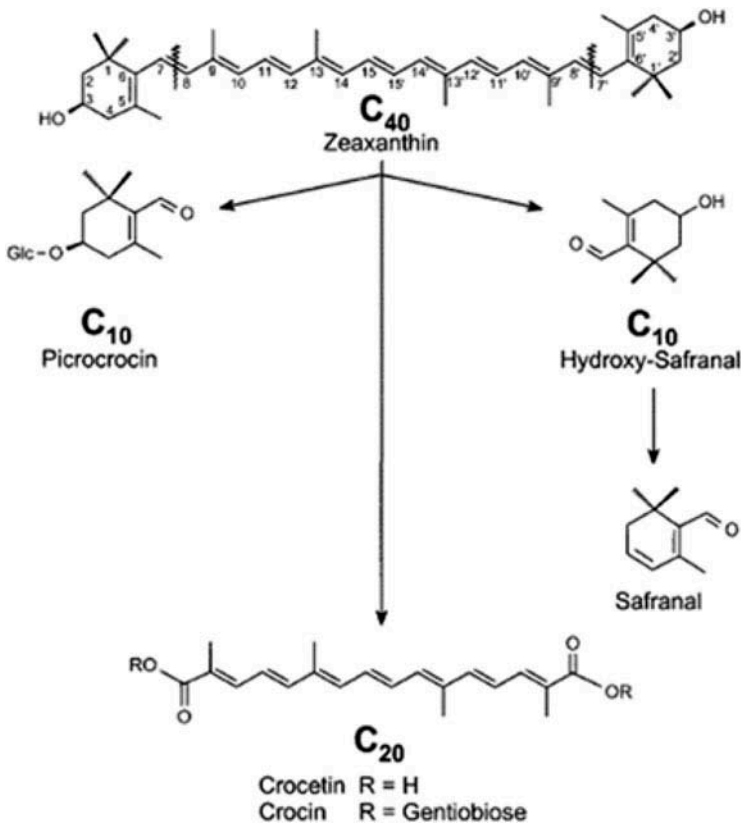

Figure 2. Cleavage of zeaxanthin produces secondary metabolites (47).

The aroma of saffron corresponds to safranal, and it is ~70% of the volatile fraction. The fresh stigma has no smell because the picrocrocin has not hydrolyzed. The absorbance of picrocrocin at 257 nm is inflated due to the interference with the crocetin ester as compared with the high-performance liquid chromatography (HPLC) data corroborated with the Fourier transform infrared analysis (17). The sharp smell of saffron appears during the drying and storage stage of saffron. The drying can cause enzymatic or thermal dissociation. The maximum UV absorption of safranal is 330 nm. Its aroma profile depends on its geographical origin, as the producing countries use different postharvesting methods; the difference lies primarily in the method of dehydration. It is important to identify the origin and mechanism by which the volatile compounds are generated (11). Crocin gives color to saffron; it is a crocetindigentiobiose ester ($C_{20}H_{24}O_4$) with a beta-shaped glycosidic bond. It is able to undergo hydrolysis by breaking the beta-shaped glycosidic bond. Crocin is a unique water-soluble carotenoid in nature. It is a water-soluble crocetin that can dissolve in water easily and produce an orange-red solution, with maximum UV absorption of 440 nm, the highest and most easily detachable among the constituents. The identification of crocetin esters is done by using a liquid chromatography-electrospray ionization-mass spectrometry method (9).

The chemical composition of saffron is determined by HPLC with diode array detection using aqueous extract as per ISO 3632. The quality of saffron (crocetin esters, picrocrocin, and safranal) can be determined using this method as suggested in ISO 3632 (21). No qualitative differences in relation to the flavonoid fraction were observed when saffron samples from different geographical origins were analyzed. This could be due to the poor genetic variability between cultivars. Difference in flavonoid profile was noted due to postharvesting methods, and and the highest flavonoid was reported for Spanish saffron (12).

Pharmacological properties and potential therapeutic application of saffron

Saffron and its active components picrocrocin, safranal, and crocin have been explored for a large number of possible medicinal usages. The pharmacological properties of active components of saffron are due to their unique chemical structure.

Diabetes mellitus

Diabetes mellitus (DM) is a metabolic disorder that occurs when the pancreas loses its ability to produce adequate insulin for the body or in some cases the body fails to use the insulin efficiently. Uncontrolled DM may lead

to high blood sugar level or hyperglycemia, which in the long term can cause severe damage to the body's systems. The World Health Organization (WHO) reports that the number of people with DM has risen from 108 million in 1980 to 422 million in 2014, and is expecting it to become the seventh-leading cause of death in 2030, leading to heart attacks, stroke, liver failure, and kidney failure. There are three types of DM (59): Type 1 (T1DM), deficient in the production of insulin by the body due to pancreatic β-cell failure, which requires daily administration of insulin and is known as insulin-dependent, juvenile, or childhood-onset; Type 2 (T2DM), non-insulin-dependent or adult-onset, characterized by a progressive decline in β-cell function and chronic insulin resistance; and gestational DM, which occurs when women develop insulin resistance during pregnancy.

Factors that contribute to DM include unplanned diet that leads to obesity. Higher body mass index (BMI) is associated with poorer metabolic control, increasing insulin resistance, greater hemoglobin A1c (HbA1c), and increased frequency of severe hypoglycemia. There are also reports of other factors such as demographic characteristics (i.e., age, sex, ethnicity), family history of diabetes, smoking, sedentary behavior, psychological stress, dyslipidemia, and rarely, social deprivation (18). The relation of systemic inflammation to diabetes for T1DM remains ill-defined, but for T2DM it has emerged as a prominent factor. Although the relation for T1DM is still unclear, there is evidence that can be accepted to relate the chronic inflammation of pancreatic islets as central to T1DM.

After a patient is diagnosed with diabetes, the treatments are based on the type of diabetes and the special condition of the patient. Tracking metabolic control from childhood until adulthood enable the prevention of T1DM, as the alteration of growth hormone/insulinlike growth factor-1 axis and abnormalities of ovarian function lead to insulin resistance. In additon, metabolic control is related to glycated HbA1c and micro-/macrovascular complication that correlates with the risk of coronary heart disease (25).

In most cases, the use of insulin has been implemented, but after blood glucose is controlled, it can be consumed by the patient where the insulin may be derived from biological sources such as cow. However, in T2DM cases there is a negative appraisal of insulin treatment known as "psychological insulin resistance" that leads to the delay of insulin initiation (26). Blood glucose control is the main defence in this disorder before proceeding to other treatment. Sulfonylureas are the oldest drugs that have been used, and in addition there are six classes of oral glucose-lowering drugs: biguanides (e.g., metformin), sulfonylureas (e.g., glimepiride), meglitinides (e.g., repaglinide), thiazolidinediones (e.g., pioglitazone), dipeptidyl peptidase IV inhibitors, and alpha glucosidase inhibitors (e.g, acarbose) (59). There are also reports on the use of metal drugs in several treatments such as for diabetes, cancer, rheumatoid arthritis, and inflammatory and cardiovascular

disease. In diabetic cases, metallopharmaceuticals based on vanadium have potential in glycemic control, as it is hypoglycemic. Other than that, metaformin and its derivatives such as metforminium decavanadate (MetfDeca) have better intracellular biochemical behavior and in recovering lipid and carbohydrate levels. Metaformin may have some side effects such as risk of lactic acidosis, vitamin B_{12} deficiency, gastrointestinal side effects, and chronic kidney disease (57).

There are reports on *Trigonella foenum-graecum* (funegreek) that demonstrated antidiabetic properties by altering levels of malondialdehyde (MDA), 4-hydroxynonanal (4HNE), superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT) in tissues (53). *Bougainvillea spectabilis* leaves reduced hyperglycemia and hyperlipidemia level along with antioxidant activity which make it a potential candidate for DM treatment (13).

Saffron has been studied as a potential candidate drug for DM. The major active constituents that give antidiabetic response are crocin, crocetin, and saffranal which display insulin-sensitizing effects that will not have any significant effect on blood serum glutamic oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), and creatinine levels (32). The main hypotheses for the modes of saffron on its inhibitory effect on free-radical chain reactions are its capability to modulate antioxidant gene expression and upregulate mitochondrial antioxidant genes, leading to lower mitochondrial oxygen radical generation. Results have shown that saffron stimulated the glucose uptake in skeletal muscle cells by activating 5′-AMP-activated protein kinase (AMPK) as well as improving the insulin sensitivity in glucose metabolism, preventing excess glucose accumulation in blood. Studies also report oral administration of saffron increasing serum insulin levels and reducing blood glucose levels, as well as improving the lipid profile, and liver and kidney function, of diabetic rats. Other than that, saffron is reported to increase glutathione content (GSH) and superoxide dismutase (SOD) that help in glucose reduction as well as helping in regeneration of damaged pancreas. Saffron also has antioxidant properties that can reduce not only hyperglycemia but also oxidative stress, which may give benefit toward treatment of diabetic encephalopathy (50).

Antitumor and anticancer

Cancer develops when a cell grows abnormally, which means it divides without stopping and in some cases leads to formation of tumors. There are several type of cancers, depending on the origin: leukemia (blood), carcinoma (epithelial cells), sarcoma (bone and soft tissues: muscle, fat, blood and lymph vessels, fibrous tissues), lymphoma (lymphocytes: T or B cells), multiple myeloma (plasma cells), melanoma (cells that become

melanocytes), brain and spinal cord tumors, germ-cell tumors, neuroendocrine tumors, and carcinoid tumors.

Cancer can be caused by multiple situations in which some may be infected by cancer-causing substances (carcinogens), genetics, the immune system, age, and human daily routine, which is rarely observed. Psychoneuroimmunology is study focused on psychological aspects of humans toward cancer risk, especially stress and depression effects from daily routine. Chronic stress and depression can activate the hypothalamic-pituitary-adrenal (HPA) axis, impairing immune response and enhancing development and progression of some cancers. The activation may be due to production of glucocorticoid hormones and catecholamines that interfere with the function of NF-kB, which regulates the activity of cytokine-producing immune cells and reduces the number of natural killer cell activities, causing somatic mutations and genomic instability (58).

Cancer treatment depends on the diagnosis and may include surgery, radiation, chemotherapy, or immunotherapy. Scientists are interested in combining chemotherapy with immunotherapeutic agents as a new potential approach for cancer treatment (58). Tumor vessels have permeability and retention effect due to absence of encapsulated seals compared to healthy human blood vessels, thus making development of new drugs or therapeutic agents more challenging (20).

Flavonoids are one of the chemotherapeutic agents that give positive immune effect via antioxidant, anti-inflammatory, and anticyclooxygenase activities such as epigallocatechin-3-gallate (EGCG) and apigenin. Epigallocatechin-3-gallate (EGCG), found in green tea, in combination with DNA vaccine was effective in inhibiting bulky tumor growth while replacing it with apigenin could improve multimodality treatment against progressive tumors (14). Studies also showed an excellent antitumor effect and long-term survival using cisplatin with DNA vaccines encoding calreticulin (CRT) linked to human papillomavirus type 16 E7 antigen (CRT/E7) in a preclinical model. Cisplatin is a type of chemotherapeutic agent commonly used in treating cancers such as ovarian, breast, and cervical (58).

Several isolated compounds such as flavone, carotenoids, isothiocyanates, polyphenols coumarins, α-angelica, gingerols, curcumin, and other polyphenols from plants (soy, broccoli, green tea, turmeric, tomato, saffron, garlic, and black cumin) have been reported to inhibit the growth and progression of chemically induced tumors. Saffron can be used as an agent in chemo preventive therapy. The ability of saffron to inhibit synthesis of DNA and RNA, but not protein, remove free radicals, involve the processes of conversion of carotenoids to retinoids, and promote the interaction mediated via lectins confirmed that saffron has antitumor and anticancer properties (23).

It is suggested that crocin is the major antitumor ingredient in saffron. Studies show that mice treated with crocin were 100% tumor-free, while

DNA vaccine alone led to approximately 66.7% and 33.3% treated with DNA +crocin. Furthermore, safranal also showed the capability to inhibit HeLa cell-line growth, profileration of MDA-MB-231 and MCF-7 cell lines, and suppress some biochemical markers of toxicity by diazinon. Crocetin has potential as an antitumor agent by inhibiting nucleic acid synthesis, enhancing the antioxidative system, inducing apoptosis, and hindering growth factor signaling pathways (23). Caspases and bax protein in saffron can act as a chemotherapeutic agent as it can reduce cell viability of MCF-7 cells (a common cell used for breast cancer study) and apopotic cell death treated with saffron extract (24). Saffron can be used in combination with liposome to improve its antitumor effect, as liposome serving as a host can rapidly enter tumor sites from blood.

Treatment for Alzheimer's disease

Alzheimer's disease (AD) is the most common disease among the elderly. AD, a dementia disease, can cause gradual deterioration of intellectual functions leading to the loss of ability to complete routine daily activities; the personality and behavior of patients changes as well. AD has affected 27 million people worldwide; the number is expected to increase and reach 86 million by 2050 (19).

AD is the most common neurodegenerative disorder that may be inherited directly from family. Age is the major factor, in that ~40–50% of people 85 years old face AD. Another risk factor may be an apolipoprotein E (APOE) genotype that exists in the family history, which is capable of shifting the age at onset to an earlier time point. The factor that causes AD is in the cerebral cortex; there are numerous amyloid plaques present, the main component of the plaques is amyloid β (Aβ), and the neuronal damage may be due to deposition of Aβ (2, 13). There is also evidence of genomic risk contributing as a factor for AD for variation in CLU (encoding clusterin), PICALM (encoding the phosphatidylino-sitol binding clathrin assembly protein), and CR1 (encoding complement component receptor 1).

The treatments or biological action needed may differ with the types of AD itself, depending on the onset time, which are early-onset AD (EOAD: before the age of 60 years) and late-onset AD (LOAD: after the age of 60 years). The most well established biomarkers for presymptomatic detection of this disease can be divided into two major groups depending on functionality: (1) measures of brain Aβ deposition and (2) measures of neuronal injury and degeneration. Cerebrospinal fluid (CSF) is a valid source as an AD biomarker, as well as positron emission tomography (PET) amyloid imaging, which is categorized as the first group (19, 30). The second group is more focused on CSF tau (total and phosphorylated tau), fluorodeoxyglucose (FDG) PET, and structural magnetic resonance imaging (MRI). Blood

analysis is advantageous because it is simple and less invasive, and an 18-biomarker panel has been identified from a group of 120 signaling proteins that can detect AD symptoms (30).

There are several methods used to treat AD, from dietary implementation to chemical and biological means, but there is no effective treatment for this disease. Indeed, there are two limitations that need to be considered to develop treatment for AD: (1) the use of drugs that are highly specific because they fundamentally may cause harm than good; and (2) delivery of drugs to the brain is more difficult than to other organs. As the neuronal damage may be related to oxidative action by free-radical species, an anti-oxidant-rich diet may able to reduce the risk of AD. Common antioxidants used are vitamin C, vitamin E, α-lipoic acid (ALA), and co-enzyme Q (CoQ), but the problem with antioxidants is in determining the right dosage. Vitamin C with the combination of vitamin E is able to reduce oxidative damage and improve performance of spatial memory. Treatments with vitamin E only will attenuate plaque formation if the treatment is started before amyloid deposits are present. Messing (2016) reported that bacteriophage M13 infects *Escherichia coli* (*E. coli*) and has been used to reverse the formation of plaques derived from amyloid-like structures in the brain and itself could reverse the aggregation of misfolded proteins (42).

Current drugs used to treat AD are cholinesterese inhibitors (donepezil, rivastigmine, and galantamine) and N-methyl-D-aspartate receptor antagonists (memantine). There are also reports combining these two types of drug to enhance the therapeutic benefit, but there are a lack of reports that show improved cognition, function, and behavior of treated patients (46). Ferulic acid (4-hydroxy-3-mthoxy cinnamic acid, FA) has anti-inflammatory and antioxidant effect plus the capability to inhibit Aβ fibril aggregation, prevent Aβ-mediated toxicity, and improve cognitive ability. Histone deacetylase 6 inhibitor (ACY-738) modulated tubulin acetylation in amyloid protein/presenilin 1, but it has seen limited progress due to low blood–brain barrier penetration (38).

Saffron has been reported to improve learning and memory properties, have a genoprotective effect, and protect from genotoxins-induced oxidative stress due to a wide range of bioactives that are present. It is a great source of carotenoids such as crocins, that is, mono- and diglycosides of crocetin (CRT), as well as a source of acetylcholinesterase inhibitors for AD treatment. Studies also revealed that saffron counteracted age-related memory impartments, improved cerebral antioxidant markers, decreased acetylcholinesterase (Ache) activity, and has effect against scopolamine-induced recognition deficits in adult mice and rats (55). Crocin enhanced learning and memory functions as well as had preventive effect on long-term potentiation (LTP) which is blocked by ethanol *in vivo*. Long-term potentiation (LTP) is a form of activity-dependent synaptic plasticity and is believed to be a cellular

basis of learning and memory in the hippocampus. In addition, crocin can be used in the ethanol inbibition of NMDA receptor activities compared to picrocrocin (1). Saffron eliminated the accumulation of amyloid β in the human brain due to the protective effect of crocin, enhancing the stability of proteins.

Cardiovascular disease

Cardiovascular disease (CVD) is a generic term that describes heart and blood vessels disease that may result from blood flow to the heart being reduced as the result of a blood clot (thrombosis) or buildup of fat plaque in walls of arteries (atherosclerosis). There are several types of CVD (55): (1) heart attack, due to blockage of blood flow to the heart by blood clot, also known as coronary heart disease that may cause angina (chest pain); (2) stroke, a medical condition where the brain is damaged or death occurs due to cut-off blood supply to the brain due to blockage, which known as ischemic stroke; (3) heart failure, also known as congestive heart failure, which means the heart is not pumping as well as it should, resulting from the insufficient oxygen-enriched blood supply to all parts of body; (4) arrhythmia, an abnormal rhythm of the heart due to electrical properties of the heart, where the heart beat may be too slow, too fast, or irregular; (5) heart valve problems, where the valve may function abnormally, such as in stenosis, where the valve may not open enough for blood flow, regurgitation, where valve does not close properly, causing backward flow of blood, and mitral valve prolapse; (6) others, referring to blockage of certain main blood vessels related to heart function, such as peripheral arterial disease and aortic disease. There are several factors that lead to CVD: high blood pressure (hypertension), smoking, high blood cholesterol, diabetes mellitus (DM), lack of exercise, obesity, family history, and ethnicity.

Diet that is recommended for a healthy heart is a low-fat, high-fiber diet and unsaturated-fat food such as oily fish, avocados, rapeseed oil, and olive oil (55). Phytotherapy is broadly defined as the use of natural therapeutic agents derived from plants or crude herbal drugs. *Ligusticum chuanxiong* Hort, *Dalbergia odorifera* T. Chen, and *Corydalis yanhusuo* WT Wang are representatives of Chinese herbs in CVD treatment in which have been identified 54 proteins of 64 bioactive ingredients closely associated with CVD (34). Consuming food rich in antioxidants such as blueberries, black plums, and prunes that contain vitamin C, carotenoids, and vitamin E may prevent atherosclerosis by blocking the oxidative modification of low-density lipoprotein (LDL). The drugs digitoxin, derived from *Digitalis lanata* or *Digitalis purpurea*, and digoxin derived from *D lanata* alone, have been used in treatment of congestive heart failure. *Rauwolfia serpentina* root is

the natural source of alkaloid reserpine, which has been used to reduce hypertension to minimize cardiac arrest (40).

Saffron was reported to be cardioprotective in isoproterenol-induced myocardial damage. A study suggest that saffron at all doses was cardioprotective by preserving hemodynamics and left ventricular functions, maintaining structural integrity and augmenting antioxidant status. Antioxidants in saffron tea (lycopene, a flavonoid) can reduce the risk of cardiovascular diseases (49). *In vitro* study demonstrated the electrical conductivity effect of saffron, which has a depressant effect on AV nodal rate-dependent properties. In high doses, saffron slowed the electrical conduction velocity in both atrium and ventricle and may help in preventing arrhythmia. It was suggested that crocetin and crocin activate different mechanisms in the vasoconstriction pathway in hypertension, treating endothelial dysfunction, especially aortic contraction problems, which is also known as having hypotensive effect (25). Saffron is hypolipidemic and can reduce serum triglyceride, total cholesterol, low-density lipoprotein (LDL) cholesterol, and very-low-density lipoprotein (VLDLV) cholesterol levels in a daily dose of 25–100 $mg.kg^{-1}$ by inhibiting pancreatic lipase, leading to the malabsorption of fat and cholesterol and enhanced reduction of CVD risk such as in atherosclerosis, hypertriglyceridemia, and hypercholesterolemia (54).

Erectile dysfunction

According to the U.S. National Institutes of Health, erectile dysfunction (ED) is defined as the inability to attain or maintain an erection sufficient for satisfactory sexual performance. In other words, ED can be considered the consistent or recurrent inability of a man to attain and/or maintain penile erection sufficient for sexual activity. There are several ways of diagnosing ED. The International Index of Erectile Function (IIEF) has been proposed as a new standard method that has been widely used to asses ED using a multidimensional scale that is more specific and sensitive for detecting changes in erectile function (EF). Nitric oxide (NO) has been recognized as a key mediator of penile erection and plays an important role in signaling smooth muscle relaxation. Now, ED is regarded as a major health problem that may rise to 322 million cases by the year 2025 (15).

There are several factors that lead to ED, including age, diabetes, cardiovascular disease, obesity, hypertension, hyperlipidemia, metabolic syndrome, depression, lower urinary tract symptoms, smoking, penile fracture, Peyronie's disease, and side effects from other drugs (15, 52). The use of several drugs can also cause erectile dysfunction: (1) antidepressants; imipramine, doxepin, isocarboxazid, protryptiline, maprotiline, amitripline, amoxapine; (2) antipsychotics; chlorpromazine, pimozide, thiotixene, sulpiride, haloperidol; (3) anthypertensives; hydrochlorothiazide, reserpine, labetol,

atenolol, guanadrel, guanethidine, reserpine; (4) drug abuse; alcohol, cocaine, amphetamines, MDMA; (5) anticonvulsants; barbiturates, phenytoin, primidone, carbamazepine; (6) other miscellaneous; ketamine, methadone, cimetidine, lithium, disulfiram, ketoconazole (15).

The treatment for ED begins with psychosexual and couples therapy for purely psychogenic ED and relationship problems, followed by lifestyle modification such as weight reduction, physical exercise, and smoking cessation, ending with testosterone supplement for associated hypogonadism. Other approaches include first line (oral medication), second line (intracavernosal and intraurethral injection, vacuum constrictive devises, gene therapy, growth factor targets, and combination therapy), and lastly (tissue engineering, regenerative treatment, cavernous muscle cell auto transplantation, neural auto transplantation, penile cartilage rods, penile prosthesis) (52).

Phosphodiesterase type 5 inhibitors (PDE5-Is) such as sildenafil, vardenafil, tadalafil, udenafil, and mirodenafil are structurally similar to cGMP and will compete for the catalytic site of phosphodiesterase type 5 (PDE5), which will slow down formation of 5′-guanosine monophosphate (GMP) from cGMP. This action leads to accumulation of cGMP in smooth muscle cells, causing relaxation outcome, increased arterial blood flow, and penile tumescence. Studies suggest the use of a combination of L-arginine glutamate and yohimbine hydrochloride will effectively improve EF in mild to moderate ED through evaluation of IIEF score and diary logs of sexual intercourse success rate. Other drugs that can be used in treating ED include dopamine receptor agonists, prostaglandin E1(PGE1) known as alprostadil, nitric oxide synthase (NOS) isoforms, papaverine, phentolamine, statin, L-citrulline, and phenylephrine (15, 43).

The synthetic drugs may cause negative side effects such as muscle pain, headache, blurred vision, dangerous interaction with other medication, and also do not increase libido. Aphrodisiacs were used a thousand years ago in Chinese, Egyptian, Greek, and Indian cultures which allowed human procreation, increased sexually fulfilling relationships, and fertility. Physiologically, these drugs enhance erection through hormonal changes, increased blood flow, and relaxation of corpus cavernosum smooth muscle tissue. Historically, aphrodisiacs are derived from *Bufo* toad, *Tribulus terrestris*, horny goat weed, MACA root, *Panax ginseng*, nutmeg, saffron, cacao, and ambrein (41).

Studies have shown that saffron has significant effect on men with ED by IIEF test and nocturnal penile tumescence (NPT), which is cheaper compared to PDE5-Is. The component of saffron that gives this therapeutic affect is crocin, especially at doses of 160 and 320 $mg.kg^{-1}$ body weight, which increased mounting frequency (MF), intromission frequency (IF), and erection frequency (EF) and reduced ejaculation latency (EL), intromission

latency (IL), and mount latency (ML). Although some studies showed beneficial effects of saffron on sexual dysfunction, long-term outcomes have not been documented (43).

Antidepressant

Depression is one of the most commonly diagnosed psychological disorders or mental illnesses, and reports have showed that one out of five adults may experience depression symptoms once in their lifetime. Depression was often considered a sign of weakness rather than a health problem that might need medical attention (8).

In the elderly, ageing-related and disease-related processes, including arteriosclerosis and inflammatory, endocrine, and immune changes, compromise the integrity of frontostriatal pathways, the amygdala, and the hippocampus, and increase vulnerability to depression. Childhood trauma has a strong link to depression due to deficits in general emotion regulation. Several treatments have been used to treat this disease, including meditation or mindfulness, a process that leads to a mental state characterized by nonjudgmental and nonreactive cognition and bodily sensation as well as external stimuli (5). Drugs have been used to relieve depression, such as neural cell adhesion molecule (NCAM) protein, citalopram HBr, and escitalopram, while other treatments may exist, for example, repetitive transcranial magnetic stimulation (rTMS) antidepressant treatment. Synthetic antidepressants may have side effects on the patient such as dry mouth, constipation, and sexual dysfunction, thus herbal drugs are a better alternative as they are safer, more tolerable, and more accepted by patients (37).

Saffron has been shown to increase oxidative stress level and decrease antioxidant defenses due to the lowering of antioxidant enzymes such as SOD, catalase (CAT), and glutathione peroxidise, as well as increasing markers of oxidative stress such as malondialdehyde (MDA) that cause depression (4). Safranal and crocin increased the CAT activity in liver tissue, and all three active components of saffron increased the SOD level and glutathione availability (28).

Depression may depend on the serotoninergic effects. The chemical properties of neurotransmitters such as dopamine, norepinephrine, and serotonin play important roles in depression. Crocin has shown antidepressant impact. A nonselective serotonin (5-HT) receptor, chlorophenylpiperazine, displayed affinity for the 5-HT2c family receptors, and research showed that crocin influenced the serotonergic mechanisms by having an antagonistic action on that receptor site and thus the serotonin uptake increased (31). Also, the effects of saffron on serotonin availability can decrease and lower premenstrual symptoms.

Antibacterial effect

Saffron has immunological function in human health by enhancing immune response against bacterially caused infection or disease. Carotenoids present in saffron increase natural killer cell (NK-cell) activity, increase lymphocyte response to mitogens, protect immune cells from their own bactericidal production of reactive species, and increase total white blood cells in HIV patients. Safranal and crocin were responsible for bactericidal effect in food contamination caused by *Salmonella* (48). Saffron petal was a effective antimicrobial in clothing and textile materials as a natural dye against *Staphylococcus aureus, Escherichia coli*, and *Pseudomonas aeruginosa* (22). The antibacterial action of different parts of the saffron plant such as stigma and callus both showed varying degrees of inhibitory effects on pathogenic bacterial strains. For example, saffron stigma extract was more effective in inhibiting *Sigella flexneri* at lowest concentration, 400 μg.mL^{-1} compared to saffron callus, 750 μg.mL^{-1} (45). The ethyl acetate extract of various parts of saffron can be active against bacteria *(Microccucos luteus, Staphylococcus epidermitis, S. Aureus*, and *E. coli*) and fungi (*Candida albicans, Aspergillus niger*, and *Cladospourium sp*.) (27).

Conclusion

This article reports the medical prospects of saffron, which has been extensively explored by scientists. Prococrocin, crocin, and safranal are the most influential bioactive components in saffron, which contribute to its health-promotion and disease-preventing properties. The challenging part is sustaining its raw production to meet demands, which makes it an expensive commodity in the market. Clinical trials are needed to ensure that there are no adverse or side effects and to determine the correct dosage for human consumption.

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