Journal of Research in Clinical Medicine

J Res Clin Med, 2021, 9: 28
doi: 10.34172/jrcm.2021.028
https://jrcm.tbzmed.ac.ir

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Review Article

Characterization and health effects of saffron in disease treatment and prevention: a review

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Article info

Article History:
Received: 19 Jan. 2021
Accepted: 8 Feb. 2021
e-Published: 22 July 2021

Keywords:
- Saffron
- Crocus sativus L
- Disease treatment and prevention
- Liver diseases
- Diabetic diseases
- Ocular diseases

Abstract

With the current technological development, finding and exploring novel chemical compounds from the natural material sources can be one of the significant purposes for researchers. Especially, saffron is known to be the highest-cost medicinal plant, a high-grade spice, and an outstanding dye. Concomitantly, the final saffron products truly affect much their quality to protect the rights for the consumer, as well as its available healthy benefits can be utilized for treating or preventing various diseases. Herein, the chemical characterization and health effects of saffron are shortly introduced and summarized through treatment and prevention of different diseases (i.e.: cancer, liver, ocular, diabetes, antidepressant, Alzheimer, and gastrointestinal diseases), which can favor readers understanding clearly the saffron advantages through this short review. Moreover, it can provide relatively for choosing an effective drying method to maintain the product qualities and facilitate the industrial production of saffron.

Introduction

As known, saffron (*Crocus sativus L.*) is originated from Iran, Spain, and other countries, which is also employed much in traditional Chinese medicine.[1-3] In particular, it is also known as one of the highest-cost medicinal plants and a high-grade spice in the world.[1, 4] which is collected basing on a manual method, and then drying (Figure 1). Furthermore, the name saffron (Arabic language) is understood to be yellow due to the color carotenoid constituents becoming an excellent dye.[5, 6] Additionally, it is often adulterated with other dyed natural material sources to reduce its costs (i.e.: lotus stamens, safflower stamens, and corn stigmas).[7, 8] So far, there are also several concerned methods whichcan control the quality and chemical compounds of saffron, protect rights for the consumer, as well as its valid benefits can be utilized for treating or preventing different diseases.[9-11] Thereby, more 150 various compounds can be exactly determined in the saffron including polypeptides, carbohydrates, lipids, minerals, H_2O, and vitamins from chemical structure analysis instruments and methods. Concomitantly, it was also found four major bioactive compounds in the saffron consisting of crocin ($C_{44}H_{64}O_{24}$), picrocrocin ($C_{16}H_{26}O_7$), crocetin ($C_{20}H_{24}O_4$), and safranal ($C_{10}H_{14}O$). Specifically, crocin contains crocetin – a central core and two sugars (i.e.: gentiobiose) in its chemical structure (Figure 2), which attributes a characteristic color for the saffron (i.e.: the crocin will be hydrolyzed as well as absorbed to be an active metabolite crocetin in the intestines). Picrocrocin is a characteristic bitter taste of saffron, while safranal is considered to be the odor and aroma of saffron being the metabolite of picrocrocin (Figure 2).[12, 13] Notably, saffron is seen as a valuable drug in medicine, which has been also used to treat various diseases in the scientific reports [14-32] (Table 1 and 2). The health benefits of saffron mostly relate to treatment and prevention of depression, heart, nervous system, endocrine system, and immunological diseases,[33, 34] which has also been employed safely in ocular disease treatments (i.e.: mild-to-moderate glaucoma and retinal maculopathy disorders) with a short-term use of saffron in recent years.[35]

Herein, the available chemical compounds and essential advantages of saffron are summarized shortly to favor readers understanding clearly the saffron applications for treating and preventing different diseases (i.e.: cancer, liver, ocular, diabetes, antidepressant, Alzheimer, and gastrointestinal diseases). Moreover, it can also be truly relevant for choosing an effective drying method to

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maintain product qualities and facilitate the industrial production of saffron, which can be seen as a necessary reference to design drying methods suitably with technical specifications, especial for precious traditional Chinese medicines.

Chemical characterization of saffron

Crocus sativus L. or saffron is known as Crocoideae – subfamily of Iridaceae family (i.e.: rich in endemic species) with the highest economic worth; however, the saffron is often adulterated with other dyed natural material sources to reduce the costs, such as lotus stamens (Nelumbo nucifera Gaertn.), safflower stamens (Carthamus tinctorius L.), and corn stigmas (Zea mays L.) with the similar appearance to saffron.[7, 8] Thus, several analysis instruments and methods have been concerned to control the saffron quality anddetermine the chemical structures in the saffron, such as traditional identification (i.e.: morphological identification, water test, and microscopic identification), high performance liquid chromatography (HPLC),[9] proton nuclear magnetic resonance (^{1}H-NMR) spectroscopy,[10] gas chromatography (GC),[11] and etc… Among them, the traditional identification has an advantage to be rapidly conducted; however, that performer is truly professional to evaluate the results, as well as the persuasiveness and accuracy are not high. Therefore, Li et al employed near-infrared (NIR) spectroscopy analysis to quantify and qualify quickly the adulteration of saffron.[36] It indicates that the partial least squares discriminant analysis (PLS-DA) could confirm a quick and exact distinction between adulterants and saffron. The synergistic interval PLS (SI-PLS) analysis was the best model for identifying the proportion of adulterated lotus stamens contained in adulterated saffron, while the competitive adaptive reweighted sampling PLS

Figure 1. Illustration flower and stigmas of saffron (*Crocus sativus L.*).

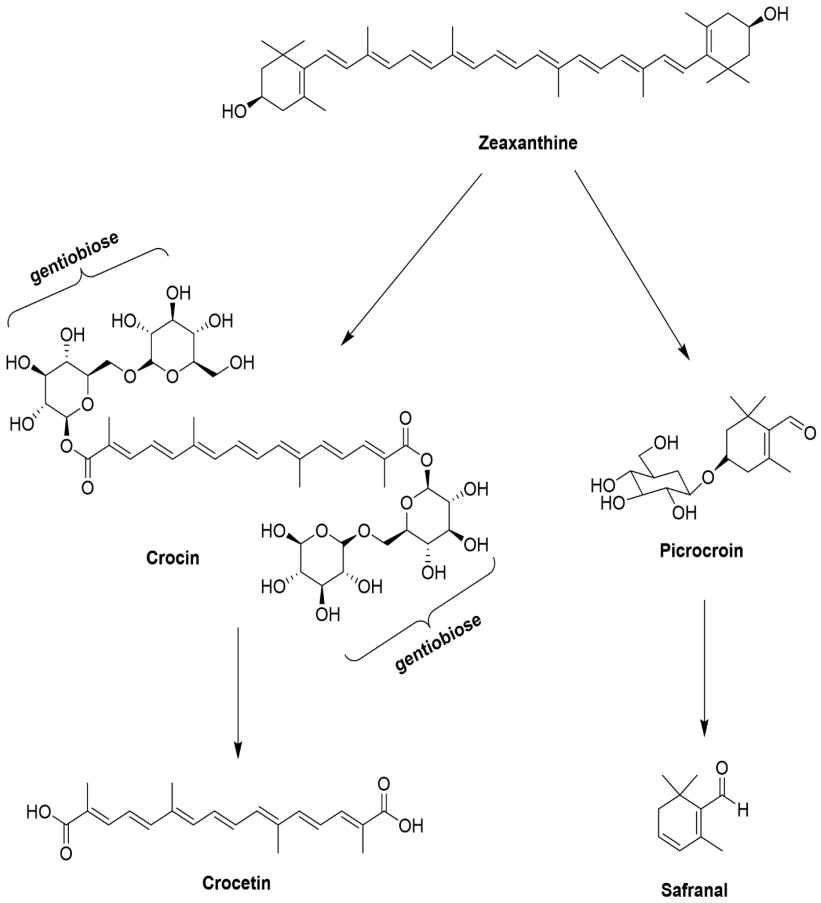

Figure 2. Possible structure of chemical compounds in saffron.

Table 1. Several common applications of saffron[15-19]

Names	Applications of saffron
Analgesic	Tooth-ache, earache, anal pain, gingivitis, cancer pain, gout, etc.
Central nervous	Neurasthenia, hypnotic, central nervous system stimulant, mental disease, anticonvulsant, sedative, etc.
Cardiovascular	Removing blockages of vascular, cardiac stimulant
Respiratory	Asthma, expectorant, pertussis, pleurisy, dyspnea, bronchitis, antitussive, disability tonsils leading to snoring, etc.
Genitourinary	Treating impotency, contraceptive, stimulate/promote menstruation, terminate pregnancy, diuretic, kidney stone, etc.
Gastrointestinal tract	Treatment of jaundice and enlargement of the liver, prolapse of anus, hemorrhoid, anti-flatulent, etc.
Infection disease	Anti-bacterial/septic/fungal, smallpox, measles, scarlet fever
Ocular disease	Painful eye, poor vision, lacrimation, corneal disease/cataract, etc.
Skin disease	Treating acne, psoriasis, wound, eczema
Others	Diaphoretic, tissue coloration, anti-cancer, etc.

Table 2. Several applications of saffron utilizing in pharmacological activities

Surveyed constituents	Studied diseases	Results
Saffron crocin	Liver enzymes[20]	Antioxidants activity decreased, liver enzymes improved.
	Liver damage (Cisplatin) [21]	Liver was protected to against cisplatin due to toxicity.
	Iron on liver[22]	Biochemical changes impacted to iron overload in rat liver.
	Liver damage (Morphine) [23]	Liver was protected from the damage due to morphine.
Extracts of saffron constituents	Nonalcoholic fatty liver[24, 25]	Hepatoprotective and hypoglycemic activities [24].
		Liver was protected to against high fat diet induced liver damage and nonalcoholic fatty liver disease [25].
	DNA damage[26, 27]	Liver was protected from DNA damage due to methyl methanesulfonate.
	Chronic stress[28]	MDA levels decreased as expectation; other levels raised total antioxidant reactivity in the stressed animals.
	Aged liver[29]	Several important biochemical substances in the liver were protected/improved aged liver.
	Diabetes[30, 31]	Glucose level of blood in diabetic rats deceased, and their liver was protected by reducing the oxidative stress.
	Liver cancer[32, 33]	Cell proliferation was impacted, and apoptosis was also induced in liver cancer cell of disease rats.
	Alzheimer's disease[75, 76]	Mild-to-moderate depression could be alleviated [76].
		Cognitive function basing on the use of saffron was caused better than placebo [75].
	Digestion[80]	Digestion was improved by increase in gastric acid and pepsin.
	Gastric ulcer [81]	Rats with gastric ulcers were alleviated as same as Omeprazole.
	Age-related macular degeneration[82, 84]	Flicker sensitivity of retinal was alleviated [82].
		Retinal sensitivity and function was improved [84].

(CARS-PLS) analysis was used to effectively determine the content of adulterated corn stigmas contained in adulterated saffron. Thereby, the NIR spectroscopy and chemo-metric methods could simultaneously combine to quantify and qualify effectively the mentioned adulterations without damaging the products. Notably, there are over 150 compounds with glycoside formation of different sugar molecules contained in the saffron (i.e.: volatiles, flavoring, and phenolic compounds) through the suggested analysis instruments. In addition to the mentioned compounds, flavonoids (i.e.: delphinidin, kaempferol, derivatives, quercetin, and etc.), fatty acids (i.e.: palmitic, linoleic acids, oleic, and etc.), and vitamins (i.e.: riboflavin and thiamine) are also detected in the saffron.[2-4] Especially, the most important compounds in the secondary metabolites of saffron are the crocin – colored compound (10%, $C_{44}H_{64}O_{24}$), picrocrocin – bitter compound (4%, $C_{16}H_{26}O_7$), and safranal – fragrant compound (70%, $C_{10}H_{14}O$) (Figure 2).[12, 13]

Furthermore, the product color has also influenced food flavor, although the flavor is primarily based on taste and odor.[37] The combination of available taste, aroma, and color in the saffron induces to form a complex flavor. Concomitantly, the crocin – colored compound in saffron has been utilized as a chemotherapeutic agent owing to its water solubility and inhibitory effect on the growth of

cells. Specifically, the crocin compounds have significantly inhibited pancreatic cancer cells, breast cancer cells, and human rhabdomyosarcoma cells.[38] The crocin compounds of saffron regard to glycoside derivatives from the carotenoid crocetin can be well soluble in water,[4, 39] as well as its content is truly important to define the saffron quality (≥10%).[2] Besides, the picrocrocin – bitter compound is saffron carotenoid and created from oxidative degradation of zeaxanthin compound (Figure 2), while the safranal – odor compound (i.e.: a volatile ingredient of saffron) is easily converted from the picrocrocin and glycosidase compounds during storage and drying processes with high temperature[3, 12] (Figure 2). Especially, saffron safranal is not only a characteristic aroma component[4] but also a biologically active component.[13]

To maintain the qualities of saffron during the storage and drying processes, it is truly concerned to pH levels and light, because its stability is not high and very sensitive to pH changes, oxidants, and light. Thus, its storage conditions are truly necessary to follow and check regularly [12]. Specifically, it actually relates to the saffron pigments following its shelf life. Since low saturated nature, crocin isomers could occur oxidation and isomerization reactions to fade in the color of the spice. For instance, Alonso et al investigated an autoxidation of saffron from different storage conditions.[40, 41] Raina et al also showed the changes of volatiles and pigments contained in the saffron during storage and processing processes.[42] Besides, Morimoto et al have studied a degradation of pigments after the saffron harvest,[43] while Tsimidou et al have investigated a stability of pigments in aqueous extracts and quality deterioration kinetics.[44, 45] These results manifest that both of humidity and temperature impact strongly on the degradation kinetics and loss pigment rate, as well as the available odor and bitter features of saffron could increase or decrease depending on the water activity. Moreover, the conditions of odor increase are unimportant for the stability of pigments. As such, the storage conditions and optimal processing parameters can support to improve and maintain the saffron quality.

Health effects of saffron in disease treatment and prevention

In general, saffron containing available natural features is concerned to be a food coloring/cosmetic source and an ornamental flower. Besides, the use of saffron mostly regards to health benefits in traditional medicine and various research purposes. As shown in Table 1, in addition to some common features of saffron, it can be modified and synthesized to develop further drugs-based pharmacological activities.[23-32, 46-49] Actually, the traditional applications of saffron were recognized much, as well as its health benefits of modern medicine. To further discovery of the useful benefits of saffron in the pharmacological field, it truly need to have a better understanding of its dynamics and evolution to easily investigate for human diseases.[50] Moreover, several studies have indicated the pharmacological applications of saffron and its purified constituents, as well as saffron extract fabrications could be investigated to find active ingredients in disease treatments, the most interested for the crocin and crocetin compounds[23-32] (Table 2). Especially, the effective chemical compounds of saffron and various disease (i.e.: cancer, liver, ocular, diabetic, antidepressant, Alzheimer, and gastrointestinal disease) treatment and prevention will be summarized shortly in this review through clinical (human) and vivo (Rats or Mice) studies (Table 2).

As known, cancer is one of the deathliest diseases to be regardless gender, age, and geographical place in the world. The efforts of researchers are always continuously practiced for finding a better cancer treatment and prevention. Nonetheless, the expected results are still yet achieved to uproot this disease. The exploration and expansion of anticancer agents have been mostly focused on cancer genes and cells. In particular, the replication mechanism is concerned as a significant key to inhibit tumor growth in cancer diseases. In chemotherapeutic drugs, they cannot be selected to the cancer cells, which could impact on other healthy cells in humans. Moreover, lots of vegetables, fruits, herbs, and spices contain important and necessary characterization to be used against the cancer.[33, 51, 52] Among them, the significant constitutes of saffron are truly attractive here, which has been used in traditional medicine to treat numerous illness and consisting of tumors. Recently, the extracts of raw saffron with antitumor features have been also investigated in both vitro and vivo studies.[53-56] For examples, the retinoids from the saffron carotenoid metabolites are outstanding to attract the potential attentions owing to its practicable anti-carcinogenic features.[57-59] It was suggested that the growth-tumor cells were inhibited thanks to the retinoids (i.e.: its derives and vitamin A), as well as their toxicities could be prevented a common therapeutically treatment in humans. Moreover, the antitumor studies of saffron crocetin derivatives indicated that it has effectively reduced those toxicities at higher doses in cancer chemotherapy, and several in-vitro studies have been conducted on the use of saffron pigments as well.[54, 55, 60] In particular, the saffron crocetin derivatives (i.e.: methylester dimethyl crocetin and dicarboxylic acid crocetin) are very effective that can inhibit the growing of leukemic cells. Hence, the saffron carotenoids could be proposed as promising antitumor agents, which can be alone or combined with other potential chemical agents to probably treat lots of cancer forms in the future. Although the chemical composition of saffron has been thoroughly studied, all just pointed at the detailed examination and explanation of the structures relating the saffron pigments. Concomitantly, the saffron carotenoids and phytochemicals with antitumor activity were thoroughly

investigated for their possible activities as well. Generally, the biological effects of saffron almost relate to the carotenoid compounds, due to their strong antioxidant activity. Whereas, free radicals have been occurred during metabolic reactions regarding the oxidation processes in our own body, as well as and the oxidation processes probably damage cells and cause several other diseases in the organs. To our knowledge, the extracts of saffron carotenoid were applied effectively more than those of safranal against the oxidation to be following: (i) interact with enzymes, and (ii) immediately suppress to reactive oxygen species.[12]

Furthermore, type 2 diabetes is one of chronic diseases with high complications and death as well. Actually, hyperlipidemia, hyperglycemia, and hypertension are the gravest complications frequently occurring in the diabetes [61]. Besides, this disease has been poorly controlled inducing several micro- and macro-vascular complications, counting retinopathy, neuropathy, nephropathy, and atherosclerosis which can risk highly for death.[62, 63] Hence, the medical activity have being frequently found to add and alternate essential drugs, especially in herbal medicine, to be employed as supporting for more effectively diabetic control.[64, 65] To our knowledge, there are also several clinical trials investigate the saffron influences on glucose and serum lipid concentrations on blood of the patients. Recently, Azimi et al surveyed several patients to follow low-density lipoprotein levels from a daily use of 3.0 gram saffron tea, suggesting that there were significant glucose changes in the blood after using the saffron tea;[66] however It is still unclear that the effect is due to saffron or tea. Besides, Samarghandian et al injected an amount of saffron liquids into diabetic rats to observe totally in hyperlipidemia, hyperglycemia, and oxidative stress.[67] Although the saffron has not influenced much on low-density lipoprotein concentrations on depressive patients ,[68] the three-month use of saffron on diabetic patients could significantly reduce fasting plasma glucose and low-density lipoprotein levels.[69] Interestingly, the use of saffron with common anti-hyperlipidemia and antidiabetic drugs has also decreased the fasting plasma glucose levels in participants with metabolic syndrome.[61] Nonetheless, the exactly-treating mechanisms of saffron impacted on the glucose and lipid levels are still not explained in detail, and the lipid changing efficacy of saffron is recognized from its availably active constituents. Among them, the saffron crocin could inhibit the pancreatic and gastric lipase activities, as well as it reduces the fat and cholesterol absorption.[70] Specifically, the use of saffron could lower content of triglycerides through suppressing the appetite and reducing the body weight.[71]

Liver diseases are often found by influences of liver enzymes, iron, liver damage (Cisplatin and Morphine), nonalcoholic fatty liver, aged liver, cancer, and etc. Recently, its grave levels are much considered as precedencies in assigning organs to conduct liver transplantation, as well as in forcing grave indexes of the disease through generally applicable, justified, and possessed variables. As known, the liver is a meaningful organ to support the body detoxification, and its function would also decrease gradually with age. Therefore, an antioxidant nutrient (i.e.: vitamins, protein, and minerals) is one of probable great diets that can prevent the diseases with aged liver. Samarghandian et al used the saffron to treat and protect effectively the aged liver on 20-month-old rats through the studied control processes of liver antioxidants, peroxidation, and detoxification systems.[28] Concomitantly, this is also helpful for using antioxidants to be a health advantageous food compound during aging. Moreover, the nonalcoholic fatty liver disease increases continuously as one of the occurring chronic liver conditions in recent, which is regarded to insulin resistance and the metabolic prognostic. Symptoms of the disease is revealed from high liver enzyme concentrations to cirrhosis and hepatocellular cancer disease. This disease is affiliated to the type 2 diabetes to be raised adipose tissues and deposited in the liver. In particular, the saffron is confirmed that it probably impacts on hypoglycemic activity and antioxidant influences, as well as the chemopreventive effects of the saffron crocins is truly helpful to against hepatocarcinogenic compounds .[72] Specifically, a deglycosylated crocin derivative (i.e.: crocetin) indicated to be inhibited on intracellular nucleic acid but there is not any impact on formation of various solid tumor cells.[73] Additionally, Konstantopoulos et al used the saffron on diabetic rats for an investigation of nonalcoholic fatty liver disease,[23] resulting that the glucose and steatosis levels of the disease rats was improved after applied treatment, as well as the saffron effectively impacted on hepatoprotective and hypoglycemia actions. In another study, Mashmoul et al conducted a comparison treating on the rats with normal condition and high-fat diets, revealing that the both extracts and saffron crocin have supported against the fatty liver of the rats with high-fat diet depending on suitable doses.[24] This result also suggests to hepatic enzyme changes and hepatic structure stabilization. In general, the saffron has been employed for protecting the liver to contribute as an anticancer agent and antioxidant from free radicals basing on the reviewed scientific reports. Concomitantly, the constituents of saffron could be seen like antitoxic agents for preventing an excessive and dangerous dose of various chemicals (i.e.: streptozotocin, cisplatin, acrylamide, morphine, and etc.),[20-22, 29, 30] which is also effective in treating the nonalcoholic fatty liver of diabetic rats.[24] As such, these studies manifest effective and potential results on animals (i.e.: mice and rats), several cell lines, and clinical trials that have been suggested to be performed on humans to prove the mentioned activities of saffron on the liver diseases. Besides, the use of saffron are truly necessary to

be deployed as well as find suitable-treating mechanisms. Nonetheless, the use of saffron for the research aim is still finite due to its high cost, in-door planting of saffron probably favor in attaining the highest saffron quality with a lower price comparing to its possibility in market.

In particular, Alzheimer's disease often occurs after 55-year age, which is also a dementia cause in the old/aging people. Akhondzadeh et al conducted clinical trials to investigate the health effects of saffron in the Alzheimer's disease treatment and prevention from mild to moderate levels (Table 2).[74, 75] It results a potential effect of saffron to treat and prevent Alzheimer's disease, because it probably inhibits the deposition and aggregation of amyloid β in the human brain being useful in Alzheimer's disease. Moreover, saffron is also a potential candidate to enhance mental health from antidepressant characterization. Specially, Hausenblas et al conducted two placebo controlled trials and three antidepressant controlled trials with use of saffron on depressive symptoms from major depressive disorder patients.[76] As a result, these clinical trials manifested that the use of saffron could effectively improve the depressive symptoms in major depressive disorder adults. As such, the clinical trials from comprehensive and statistical analyses can warrant the health effects of saffron for the major depressive disorder treatment.

Additionally, the susceptibility to intestinal diseases is seen to be an important matter. So, the herbal use can effective and useful in the treatment and prevention of the digestive diseases. Thereby, the saffron can also concerned to be a prophylactic and therapeutic agent prevent gastrointestinal tract disorders (Table 2).[77-80] Specifically, Kianbakht et al[80] conducted the studies on rats with gastric ulcers basing on the use of saffron alcoholic extract, crocin, and safranal, leading to being all useful and effective in ulcer recovery. Besides, it has also indicated that the above compounds of saffron could inhibit gastric ulcer formation basing on dosage and their antioxidant properties. Concomitantly, Xu et al[77] also studied the various dose effects of crocin on rats with gastric ulcers, indicating the damages were inhibited in the crocin group comparing to controls. While Inoue et al[78] evaluated the use of a drug containing 90 mg – a daily dose of saffron (i.e.: N-095) on rats with stress-induced gastric ulcer, resulting that this drug has inhibited the stress-induced gastric ulcer. Moreover, Nabavizadeh et al[79] also assumed the saffron could activate nitric oxide synthase and release histamine leading to secreting gastric acid and pepsin. In another word, the saffron crocin and safranal could improve gastric ulcers and facilitate food digestion, owing to antioxidant properties of these compounds. However, the clinical trials are truly important to various effective aspects of saffron involving different parts of the body to investigate in detail this disease. In another word, the clinical trials can provide and create new knowledge about unclear aspects of saffron effects as well as its biological compounds to be used treatment and prevention of various diseases and disorders in the future.

For ocular diseases, the carotenoids are fabricated from chromoplasts and chloroplasts containing in the plants, while the hydrophilic and lipophilic carotenoids are available in the saffron to be the most active compounds for treating ocular diseases (or lots of other diseases). For glaucoma and macular degeneration regarding the aging, the active compounds of saffron are applied effectively to treat these ophthalmological diseases to be the saffron crocins (i.e.: water-soluble carotenoids); besides, the activities mentioning ocular diseases have been conducted effective investigations in vivo, in vitro, and in clinic.[12, 81, 82] In particular, early age-related macular degeneration is considered as a macular degenerative disease by druse with large and soft characterization, retinal pigment epithelium with hyper-/hypopigmentation, as well as a moderate loss of central vision. For the randomized clinical trials, Falsini et al[81] and Piccardi et al[83] evaluated the health effect in a short-term and long-term use of saffron for this disease, respectively, owing to available antioxidant carotenoids crocin and crocetin in the saffron (Table 2). These results indicated that the use of saffron could improve retinal flicker sensitivity and macular function in this disease. Besides, Broadhead et al[84] also conducted a randomized clinical trial as well as an entire assessment in mild/moderate age-related macular degeneration treatment involving to the effectiveness and safety of oral saffron – a natural antioxidant. Resulting that the use of saffron modestly improved the visual functions in these patients; concomitantly, the longer-term use of saffron probably result better the health benefits for the patients due to its chronic nature. Overall, the saffron compounds containing crocetin, crocin, picrocrocin, and safranal have been contributed well in procedural cytotoxicity analysis. In the present work, Escribano et al investigated effectively the influences of mentioned compounds on the growth of human cervical carcinoma cells.[85]

Conclusion

In summary, the saffron is a valid herb with a long history of utilizing. Several studies have been also conducting to appreciate its beneficial effects on the liver (i.e.: liver enzymes, iron on liver, liver damage (Cisplatin and Morphine), nonalcoholic fatty liver, aged liver, liver cancer, and etc.), especially for liver cancer. Besides, the activities of saffron almost base on the crocin, crocetin and safranal. Among them, the saffron carotenoids are created from zeaxanthin, and which are important compounds involving antioxidant properties for ocular diseases. Notably, the research results have also effectively achieved in the diabetic disease treatment (i.e.: glaucoma and maculopathy diseases involving diabetes and age, age-related macular degeneration). Furthermore, the actively available constituents of saffron (i.e.: crocin, crocetin and safranal) can also play as a therapeutic and preventive role

in the antidepressant, Alzheimer's and gastrointestinal diseases, as well as these active functions have contributed to antioxidant, anti-apoptotic and so on. Concomitantly, long-term human studies should be suggested and recommended further in the future.

Competing Interests
The authors declare that they have no competing interests.

Ethical Approval
Not applicable.

Authors' Contributions
All authors have contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Acknowledgments
The authors thank the regularly updated useful information, lectures, and articles of scientists, as well as the support of Qui Nhon City Hospital.

Funding
None.

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