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Pharmacological Active Crocin (Antioxidant) in Saffron: A Review

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Abstract: *Crocin is a bioactive molecule water soluble and found naturally in numerous medicinal plants, including saffron, and is classified as a stigma in the Iridaceae family. As a known drug because it contains 150 compounds such as Crocin has been added to a variety of food items to prepare wholesome meals after drying, it can help with food product stability. Crocin is becoming more popular in the pharmaceutical industry because of its ability to protect against brain diseases and protect humans against oxidative stress so, it contains antioxidant, anti-inflammatory, anticancer, and antidepressant effects. Crocus sativaus is a phytochemical that includes three compounds: crocin, picrocrocine, and safranal, depending on there, the capacity of stigma extract to lower OS in bacteria, yeast, and plants were also evaluated, those compounds responsible for color, bitterness, and aroma in saffron. The findings showed that stigma extract reduced protein, lipid peroxidation, and chlorophyll degradation caused by methyl viologen. Plants oxidize, which increases their ability to withstand stress. It has also been demonstrated to increase yeast and bacteria's resistance to H2O2-mediated oxidative damage. Even though it is the most important drug for decreasing diabetes and obesity. Crocin significantly inhibits the growth of cell lines originating from the great majority of human cancers. Crocin is frequently used to treat stress problems associated with oxidative stress since it is a well-known potent antioxidant. It plays a role in preventing stress resulting from oxidation inside cells. Crocin is also considered one of the most important antioxidants found outside the cell. It is a strong and direct antioxidant and a protective factor against damage resulting from internal oxidation of nucleic acids. The object of this study is to use the antioxidant crocin in the pharmacological treatment of different kinds of diseases.*

Keywords: *Crocin, antioxidant, antimicrobial, saffron, and carotenoids.*

1. Introduction

Oxidation is one of the breakdown mechanisms of proteins in food[1][2]. Oxidation is an important mechanism many biological organs use to create energy, making it vital to many species. However, the excessive creation of free radicals so free radical is an able-to-survive molecule with an unpaired electron in an atomic orbital [3], caused by pollution, pressure, and smoking is extremely harmful to the body. This oxidative process not only speeds up aging but also forecasts the start of several illnesses, including rheumatoid arthritis, HIV infection, Alzheimer's, and cancer[4]. Free radicals are harmful because they may chain reactions that destroy organisms. Antioxidants have been the focus of a lot of scholarly studies to minimize oxidative damage in humans. A wide amount of empirical research reveals that natural extracts, in general, have strong antioxidant activity, therefore presenting a potential novel source of antioxidants[5]. An antioxidant is any chemical that, when present at low quantities relative to an oxidizable substrate, slows or stops its oxidation and a free radical is an able-to-survive molecule with an unpaired electron in an atomic orbital. Antioxidant action mechanisms can include removing oxygen, scavenge reacting oxygen/nitrogen species or reducing ROS/RNS manufacturing, binding metal ions needed for ROS catalysis, and up-regulating endogenous antioxidant defenses[6]. ROS, reactive nitrogen species, and reactive carbonyl species from metabolic or environmental processes cause oxidative stress in the body[7][8]. Antioxidants have been shown to play an important role in the body's defensive system against reactive oxygen species (ROS)[9].

Crocin is a significant and active compound extract from saffron[10], it is mentioned in human clinical trials [11], and it is produced only from saffron in a specific quantity[12]. Saffron (Crocus sativus) is a monocotyledonous plant belonging to the Iridaceae family[13][14][15][16]. It's been growing and consumed like a drug and spice for a long period in the Mediterranean, and Central Asia[17][18], and then It's one of the most costly spices in the world [19]. Growing countries of saffron are Iran, Greece, Italy, Spain, and India[15][20]. Furthermore, the red dried stigmas of Crocus flowers contain many compounds such as crocin, picrocrocin (carotenes such as crocin, crocetin, α-carotene, β-carotene, and lycopene), and safranal all of them called saffron however the color saffron is related to crocin [21][22][23].

The chemical compound of saffron is around 150 such as carotenoids, flavonoids, monoterpenes, flavonoid glycoside, amino acids, alkaloids, monocyclic aromatic hydrocarbons, and monoterpenoid derivatives [24][25][26]. Crocins are a colorful group that are common in saffron[27]. They have seven conjugated double bonds and are tetraterpenoid compounds[28][29] In addition to its impact in memory and learning saffron possesses anti-inflammatory, anticancer, anti-angioge effect breast cancer and antidiabetic properties[30][31]. Saffron's active ingredients, crocin, picrocrocin, and safranal are responsible for its pharmacological properties. Diabetes may be treated with saffron, according to the evidence. Hyperglycemia has revealed that saffron's active ingredients influence several signaling pathways to provide antioxidant benefits[32]. The components that give stigma its color, flavor, and aroma crocin, picrocrocin, and safranal—determine the worth and cost of saffron. As a crocetin ester (CE) generated from carotenoids, crocin is the primary secondary metabolite found in saffron. There are two isomers of crocetin ester: trans and cis. The trans isomer has more pharmacological value than the cis isomer[33][34]. The stigmas contain a number of volatile and nonvolatile compounds, as shown by phytochemical investigation. Four primary bioactive components of saffron are crocin, crocetin, picrocrocin, and safranal[34][35][36], in addition to minerals, zinc,proteins, sugar, and vitamins C, B1 and B2[4]. The carotenoid substances that give saffron its yellow color are crocin and crocetin[37]. Picrocrocin is responsible for the flavor of saffron, whereas safranal is in charge of its distinct odor. Safranal is effective in treating a number of illnesses in addition to being used as a culinary spice[38]. The main goal of this investigation was to ascertain the antioxidant content of crocin and its medicinal applications in treating certain diseases and also to assess the antioxidant capabilities of Crocus corms, drawing comparisons with those observed in the stigma. Investigations were conducted to explore the impact of saffron on preventing oxidative stress, examining its effects on both plant and microbial systems, including bacteria and yeast.

1.1. The Chemical structure of crocin

The primary pigment of saffron, Crocus sativus, produces this water-soluble carotenoid, giving its crystals a red hue [39]. When compared to gallic acid, vitamin C, and kaempferol, Crocin has been found to have greater radical scavenging steps and potential as an antioxidant. It has a main role in neutralizing free radicals, which originates with its hydroxy and glucose molecules, which function as excellent electron donors, interacting with free radicals, and contributing to its vital antioxidant ability [40].

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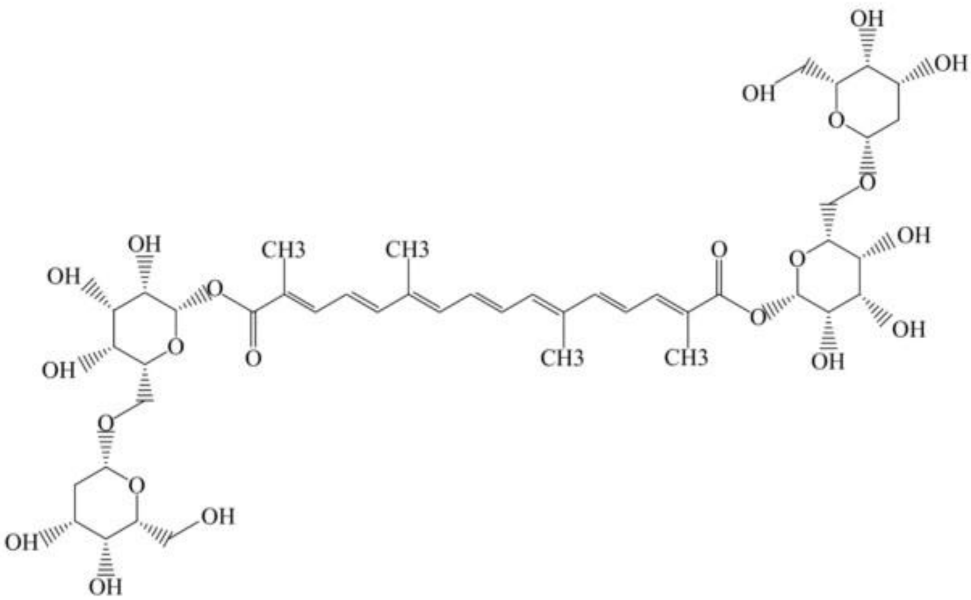

Fig. 1. The structure of crocin.

A particular kind of crocin aglycone that occurs naturally in saffron is called crocetin. Crocin hydrolysis is a biological process that produces crocetin as a bioactive metabolite. Four side-chain methyl groups, seven conjugated double bonds (both cis- and trans-form), and a polyunsaturated conjugated acid structure make up crocetin ($C_{20}H_{24}O_4$; molecular weight: 328.4 g/mol). It is sensitive to changes in pH, light, and heat due to its long chain of conjugated carbon-carbon double bonds. It oxidizes and isomerizes when exposed to heat and light. Esterification using glucose, gentiobiose, or other common sugar moieties is usually used to stabilize it. [41]. Their colors are caused by crocins, which are polyene dicarboxylic acid mono and diglucosyl esters of crocetin, which are present in gardenia and saffron. China uses gardenia fruits to manufacture herbal colors and treatments. The disaccharide gentiobiose and the dicarboxylic acid crocetin combine to form crocin, a chemical diester. Crocins are glycosyl esters of crocetin that are produced by esterification of crocetin from various glycosides, particularly geometric isomers. Crocetin molecules are moved by the action of glucosyltransferases, adding varying amounts of glycosidic to form crocins, a crucial component of saffron that provides water solubility. Most of its value is derived from crocins [42].

Crocins can be divided into four kinds, with almost all of them (save Crocin-1) being cis-trans isomeric. Many studies have shown that Crocin offers several therapeutic characteristics, such as anti-inflammatory, antioxidant, renoprotective, anti-atherosclerotic, antidepressant, anti-platelet collection, and anti-cancer activity. Crocin scavenges free radicals and helps protect cells from oxidative stress. Crocin regulates cellular protection by enzyme activity regulating and the level translation of the cellular oxidative defense system. It affects important enzymes such as glutathione S-transferase, glutathione peroxidase, superoxide dismutase, and catalase (CAT), contributing to cellular defense against reactive oxygen species. The

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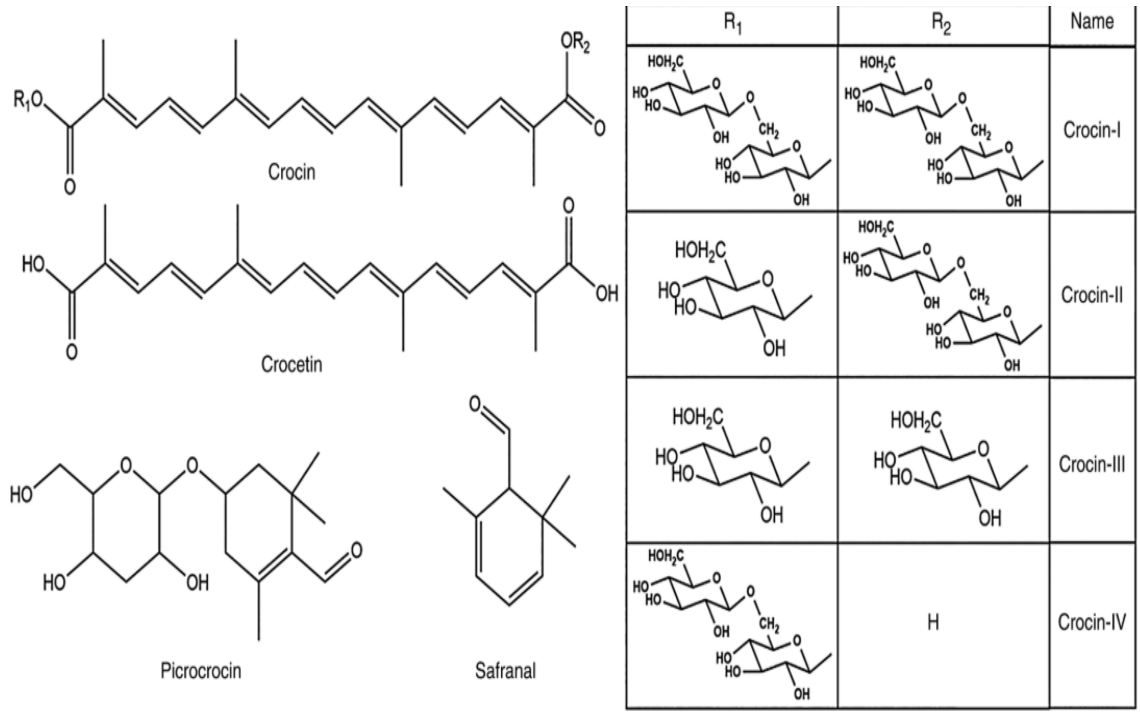

Fig. 2. The structure of saffron constituents.

endoplasmic reticulum is critical for cellular defense under stressful circumstances. convert in the mRNA levels, stressors of ER that include XBP-1/s (X-Box Binding Protein 1), BiP (binding immunoglobulin protein), PERK (protein kinase R-like endoplasmic reticulum kinase), and CHOP (C/EBP homologous protein) have been linked to several stress-related diseases, containing cancer and Alzheimer's disease. Crocin strongly enhances ER enzyme mRNA expression levels, which contributes to ER induction and, as a result, reduces oxidative stress. In addition, it causes the release of ROS species and the creation of pro-inflammatory chemicals [40].

1.2. Crocin acts as an antioxidant and antibacterial

Oxygen species that react are products of metabolism in cells that may upset redox equilibrium. Because most Apoptotic pathways and systems that respond to the stress of signaling are sensitive redox, changes in intraocular redox may impact a range of cell activities, (2,2-diphenyl-1-picrylhydrazyl) scavenging of a free-radical experiment to show the effect of safranal and crocin indicated that These substances can give a hydrogen atom to the radical of DPPH. Using safranal and crocin substantial scavenging of activities free-radical 34% and 50% for 500ppn solution in methanol, respectively [43]. Scavenges free radicals of Crocin (which include anions of superoxide), and may act as an antioxidant. Crocin can be helpful for sperm cryopreservation and saving hepatocytes from positions. Due to it is strong antioxidant capabilities, it may be effective in the treatment of neurological diseases. Changes in translation and activity enzyme levels in the cellular system redox, such as glutathione S-transferase, glutathione peroxidase, catalase, and superoxide dismutase, are identified as potential routes [43].

1.3. Crocin and Stigma Extract Play a Role in Synaptic Transmission.

These are naturally produced carotenoids found in saffron's dried stigma. They have various esterified saccharides on a crocetin backbone, such as trans-3-GG, trans-2-GG, and trans-4-GG. Crocin's glycoside carotenoid composition gives saffron its brick-red color. Furthermore, the principal of this plant may stem from its anti-anxiety, anti-convulsant, and hypnotic characteristics. Crocin, crocetin, and other bioactive chemicals are known to have antioxidant properties, which may help explain their neuroprotective advantages [15].

1.4. Several pharmaceutical treatments for depression consuming Crocin

These activities have been proposed to contribute to the antidepressant-like effects. In the next part, we'll look at these potential remedies and how saffron affects moderate mild, and serious depression. The increase in herbal therapies for depression is expected to exchange the longtime dependency on artificial antidepressants. For instance, saffron has garnered recognition as a natural resource for alleviating the symptoms of depression. Research indicates that the impact of saffron's stigma is comparable to chemically derived antidepressants for mild to moderate depression, imipramine and fluoxetine are recommended. Similarly, saffron reveals equal effectiveness to a major depressive disorder citalopram with anxious distress and indicates a decrease in mild to severe generalized anxiety disorders when compared to sertraline[15].

Saffron's pharmacological characteristics are linked to its active components, which include crocin, picrocrocin, and safranal. Saffron has been linked to the treatment of diabetes. As previously indicated, hyperglycemia is linked to oxidative stress. Investigates have indicated that saffron and its active components have antioxidant impacts by modifying numerous signaling pathways. Crocin enhances peripheral Insulin sensitivity and grows in insulin-dependent cells such as adipose cells, tissues muscular, and the heart via phosphorylating acetyl cocarboxylase and mitogen-activated protein kinases. It enhances β-cell function, decreases blood sugar levels, and inhibits diabetes-induced apoptosis in pancreatic β-cells via down-regulating the p53 protein. Furthermore, saffron and its active constituents activate the Akt kinase signaling pathway, resulting in [12].

Overweight is a growing health concern that has emerged as a major risk factor for a variety of noncommunicable illnesses, including diabetes type 2, hypertension, coronary heart, stroke, and some malignancies. According to the World Health Organization, 39% of adults aged 18 and over are obesity, with 13% being obese. While physicians frequently advise obese patients to change their diets and engage in more physical exercise, reaching a healthy body mass index (BMI) is not always possible. As a result, introducing anti-obesity drugs, such as sibutramine (serotonin and noradrenaline inhibitor) or orlistat (pancreatic lipase inhibitor), may be essential. However, extended use of these medications in obese people might result in gastrointestinal problems, low-density lipoprotein, and raised blood pressure and pulse rate. There is an increasing interest in investigating natural compounds, particularly those produced from plants, as potential therapies for overweight. Saffron's bioactive compound, crocin, has been investigated in studies to dramatically lower food use, body weight increase, total fat pad, epididymal fat weight ratio to the body, plasma triacylglycerol, and total cholesterol in obese rats. Despite these encouraging discoveries, the mechanisms behind saffron's anti-obesity benefits are still poorly understood. As a result, more preclinical studies are required to reveal the full potential of saffron as a source for creating effective and safe anti-obesity medicines[44].

Several health problems, including type 2 diabetes mellitus, coronary heart disease, sleep apnea, cancer, and liver disease, are significantly increased by extreme weight and obesity, nonalcoholic fatty liver disease, is a common liver disease that affects people who are overweight. Unusual triacylglycerol buildup in liver cells, which results in hepatic steatosis, is a hallmark of nonalcoholic fatty liver disease. Liver fibrosis, cirrhosis, non-alcoholic steatohepatitis, and rarely liver cancer are more serious liver illnesses that can develop from this illness.

Human investigations have indicated that steady weight and moderate, persistent, loss can lead to improvements in liver biochemical and histopathological profiles. Given the connection between hypertriglyceridemia, insulin resistance, and, lipid-lowering drugs that enhance insulin resistance have shown promise in reducing hepatic steatosis. Additionally, antioxidants play crucial roles in disease prevention, although further in-depth investigations are needed in this regard [45][12][46].

1.5. Molecular mechanisms of crocin's anticancer properties

1.5.1. Prevention of cancer cells from proliferating

Numerous investigations have demonstrated that crocin significantly inhibits the growth of cell lines originating from the great majority of human cancers. Remarkably, crocin had no discernible impact on the proliferation of noncancerous cells. Additionally, crocin has been shown in many in-vivo investigations to have an anticancer impact on a variety of malignancies, including stomach and breast cancers, in animal models [47][48].

1.5.2. Inhibition of DNA and RNA synthesis

The inhibition of DNA and RNA synthesis is another explanation for crocin's effects on cancer cells. It has been established that significantly crocin lowers the RNA and DNA content of a human tongue cancer cell line (Tca8113); this decrease is one of the main causes of apoptosis in this cell line. Several human cell lines, including lung adenocarcinoma, SV40-transformed fetal lung fibroblasts, K569, and promyelocytic leukemia HL-60 cells, also supported this result. However, the precise mechanisms via which crocin controls the production of DNA and RNA are yet unclear[47].

1.5.3. Oxidative stress reducing

Crocin is frequently used to treat stress problems associated with oxidative stress since it is a well-known potent antioxidant. Understanding how antioxidants work is essential for cancer treatment since reactive oxygen species have been related to the genesis of cancer by causing cellular damage. Crocin has a high free radical scavenging ability, as measured by the DPPH (1, 1-diphenyl-2-picrylhydrazyl) test. Crocin at a concentration of around 500 lM was shown in experiments to considerably reduce ROS formation after The myeloma cell line U266B1 was treated for 24, and 48 hours. modifications to the genes involved in the cellular redox system, such as glutathione S-transferase and peroxidase, and their mRNA expression. Additionally, transcriptional alterations of the stress indicators XBP-1/s, BiP, PERK, and CHOP are associated with many stress-related disorders, including cancer; there is a significant association between the endoplasmic reticulum and the oxidative stress state of cells. By modifying gene expression, crocin has been found to reduce ER-inducing stress. The reduction in nitric oxide and malondialdehyde levels in brain cell membranes suggests that it also lessens stress caused by free radicals. According to other research, crocin treatment lessened the harm that oxidative xenobiotic drugs caused to the liver. One well-known vulnerability of sulphhydryl (SH) groups to oxidative sensitivity to oxidative stress diminishes after tissue damage, indicating crocin's impact on the concentration of total thiols [47].

1.5.4. Industry and Therapeutic Activity Application of C. sativus in Herbal Medicine

C. sativus' bioactive chemicals offer several health benefits and are widely used. They are utilized in a variety of sectors, including pharmaceuticals, cosmetics, dairy, and foods. Additionally, the production of nutraceuticals and nanotechnology—including nanomedicine and nanocosmetics—uses these phytochemicals. In addition, they are employed in genetic research, cosmetic marketing, adjuvant therapy, chemopreventive treatment, therapeutic practice, and transgenic plant manufacturing. The effectiveness of pharmacological physiologically active chemical compounds from different organs of saffron crocus in the treatment of certain conditions is now being investigated through several research, cell line studies in various biological models, and clinical trials. disorders. These chemicals exert a broad range [49]. Commonly consumed saffron as a culinary coloring and flavoring component. Crocins' biological and physiological properties have been studied in the scientific literature, including their hepato-, nephro-, cardio-, and neuroprotective effects. Furthermore, these compounds demonstrate significant Further to their wide range of therapeutic effects, they have anti-cancer, anti-inflammatory, anti-hyperlipidemia, and anti-Alzheimer properties. Additionally, these chemicals have been shown to have beneficial effects on conditions connected to oxidative stress, burning mouth syndrome linked to

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anxiety and/or depression, diabetes caused by streptozotocin, and osteoporosis caused by metabolic syndrome. Because they include antioxidants, natural plant extracts may eventually take the place of artificial additives. This final product gains value from these extracts. A material with or without nutritional value that is purposefully added to food for technical, health, organoleptic, or nutritional reasons is referred to as a food additive by the FAO-WHO committee. The application of it must enhance the final product's attributes while posing no health risks at the applied dosages. Furthermore, the saffron stigma-formulated cookies had an excellent sensory score, stronger antioxidant capabilities, and a long shelf life. A compound with or without nutritional value that is intentionally added to food for technical, health, organoleptic, or nutritional purposes is referred to as a food additive by the FAO-WHO committee. When used at the recommended levels, it must improve the quality of the final product without endangering health. Additionally, the saffron stigma cookies showed a respectable improved antioxidant qualities, a decent shelf life, and a sensory score [49].

Crocin is both a great colorant and an antioxidant, squelching free radicals and protecting cells and tissues from damage. Picrocrocin and safranal are the key components that contribute to saffron's scent and flavor[50].

2. Conclusion

The present study examines the pharmacological effects of crocin extract found in functional foods as a potential treatment for various diseases. Saffron stigma contains the biologically active compound crocin. The stigma of saffron is frequently employed as an aroma and coloring agent in a variety of culinary dishes, such as drinks and baked goods. Because crocin is an antioxidant, it may slow down the oxidation process in a variety of meals. Particularly helpful in lowering the risk of illness and enhancing population health are these products containing saffron. Alzheimer's, Parkinson's, and ischemic brain are a few brain-related illnesses where crocin may be helpful. It also has the potential to prevent a wide range of illnesses and infections in humans caused by free radicals since it includes antioxidants that shield cells from harm and single electrons; several studies have demonstrated this. However, it is very expensive and spicy but it is used as a treat for human diseases, It is also very useful as a feed additive for animals and poultry as a powerful antioxidant to protect cells from oxidative damage.

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