Review

Anti-Depressant Properties of Crocin Molecules in Saffron

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Abstract: Saffron is a valued herb, obtained from the stigmas of the C. sativus Linn (Iridaceae), with therapeutic effects. It has been described in pharmacopoeias to be variously acting, including as an anti-depressant, anti-carcinogen, and stimulant agent. The therapeutic effects of saffron are harbored in its bioactive molecules, notably crocins, the subject of this paper. Crocins have been demonstrated to act as a monoamine oxidase type A and B inhibitor. Furthermore, saffron petal extracts have experimentally been shown to impact contractile response in electrical field stimulation. Other research suggests that saffron also inhibits the reuptake of monoamines, exhibits N-methyl-D-aspartate antagonism, and improves brain-derived neurotrophic factor signaling. A host of experimental studies found saffron/crocin to be similarly effective as fluoxetine and imipramine stimulation. Other research suggests that saffron also inhibits the reuptake of monoamines, exhibits N-methyl-D-aspartate antagonism, and improves brain-derived neurotrophic factor signaling. A host of experimental studies found saffron/crocin to be similarly effective as fluoxetine and imipramine.

Keywords: Crocus sativus; saffron; crocin; natural anti-depressants; traditional medicine

1. Introduction

Dried stigmas of the perennial flower Crocus sativus Linn (Iridaceae) produce a valued herb: saffron. Dubbed as “red gold” and “golden condiment”, saffron has been named in cookbooks and pharmacopoeias throughout history and geography, including Ebers papyrus (Egyptian, 1550 BC), Apicius (Roman, 1st century), Materia Medica (Greek, 1st century), Avicenna’s Canon of Medicine (Persian, 11th century), and Indian Ayurvedic literature [1–5]. Furthermore, it also serves as a dye in food products and textiles and as an aromatic in perfumes and cosmetics. These dried floral constituents most often are the vibrant stigmas of the flower, but sometimes also include styles and other floral tissue (e.g., filaments) [6]. The herb is of a red color and has a bitter taste and a pleasant fragrance. It has been employed in traditional medicine as an anti-depressant, anti-carcinogen, and stimulant, along with a great host of other functions [1,7].
Saffron is presently cultivated in Iran, India, Spain, Russia, and many other countries [6,7]. Geography varies widely, spanning Eurasia and including some of Africa. The saffron is sterile through its polyploidy, and propagation only occurs vegetatively via the daughter corms. Because of this asexual reproduction, no breeding efforts can be employed, limiting improvements to the selection of advantageously mutated corms. Only slight morphological and biochemical differences exist between these clones geographically. Morphological abnormalities rarely occur. This usually manifests in more or less than three-branched stigmas, through the fusion of flowering buds [8]. Saffron’s value is tied to its limited production methods. Harvesting is a laborious manual process and difficult to mechanize [9,10]. Saffron flowers in the autumn. Harvesting is only possible upon first bloom, as the frost of the superseding night will damage the flower. Therefore, harvesting is only done on a per flower basis. The subsequent separation of the styles and stigmas is most often also manual work, where the worker must regard not damaging the herb.

Ancient civilizations recognized saffron’s multitude of therapeutic effects. Second millennium B.C. Assyrians and Babylonians employed saffron as a medicine against dyspnea, neurological disorders, menstruation, and painful urination [11]. The Greeks used saffron against insomnia, addiction withdrawal, and hangovers [1]. The Egyptians used it as an incense with sedative qualities [12]. Saffron’s therapeutic effects are copious, as will become apparent from Table 1.

| Function                  | Experimental Findings                                                                 | Reference |
|---------------------------|--------------------------------------------------------------------------------------|-----------|
| **Diuretic agent**        | Doses of 120 and 240 mg/kg BW have been shown to have diuretic activity in rats, however, at lower activity than hydrochlorothiazide. | [13]      |
| **Analgesic agent**       | Safranal, ethanolic, and aqueous saffron extracts acted as analgesic agents in animal models. | [14]      |
| **Anti-nociceptive**      | Aqueous saffron extracts reduced pain in rats during the chronic phase of formalin test, in a dose-dependant manner | [15]      |
| **Anti-inflammatory**     | Ethanol saffron stigma extracts exhibited edema inhibition, with similar coagulation time to aspirin. | [17]      |
| **Anti-convulsant**       | Aqueous and ethanolic extracts of stigmas and petals reduced pain signaling from acetic acid-induced writhing. | [16]      |
| **Bronchodilatory**       | Concentrations varying between 4 and 16 mg/mL of saffranal had a preventive effect on the tracheal responses in guinea pigs | [19]      |
| **Secretagogues/anti-diabetes** | A combination of resistance exercise and 40 mg/kg/day of saffron administration improved diabetes’ parameters, including insulin release and glucose uptake, in rats. | [20]      |
| **Hepatoprotective**     | 20 mg/kg doses of saffron petal hydroalcoholic extracts reduced acetaminophen-induced liver toxicity in rats. | [21]      |
|                           | 100 mg/kg doses of saffron hydro- and alcoholic extracts prevented liver injury in rabbits with prolonged exposure to amiodarone. | [22]      |
|                           | 80 mg/kg ethanolic extracts of saffron significantly reduced hepatic injury biomarkers during exposure to rifampin. | [23]      |
| **Anti-carcinogenic**     | Aqueous saffron extracts achieved a chemopreventive effect in mice. However, this was not consistently dose dependant. | [24]      |
Table 1. Cont.

| Function               | Experimental Findings                                                                                                                                                                                                 | Reference |
|------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Neuroprotective        | A 6.5 mg/kg per os saffron extract reduced depressive-like behavior in mice during forced swimming. This was suggested to be related to increased monoaminergic neurotransmission activity.                                    | [25]      |
|                        | The 20, 40, and 80 µg/mL ethanolic saffron extracts increasingly significantly reversed 500-µM corticosterone-induced PC12 cell death.                                                                                   | [26]      |
|                        | At 1280 µg/mL, extracts progressively increased cytotoxicity.                                                                                                                                                           |           |
| Withdrawal management  | Daily doses of 60 mg/kg i.p. saffron extract reduced severity of withdrawal manifestations in adult male rats.                                                                                                           | [27]      |

The present study provides an overview of saffron and its constituent crocin as an anti-depressant in historic medicine and the respective modern evidence. To this end, Scopus and Google Scholar were queried for reports on the pharmacological activities of saffron constituents, with particular focus on crocin, relating to mechanisms pertaining to depressive disorders. Additionally, the bioavailability of crocins and delivery mechanisms were investigated.

2. Depression and Associated Disorders and Role of Natural Products as Adjunct Therapy

Depressive disorders are a group of emotional states centering around sadness. These range in severity, varying between unhappiness and discontent to a debilitating state of despondency [28]. Two predominant depression disorders are persistent depressive disorder (PDD) and major depressive disorder (MDD). PDD, or dysthymia, typically endures longer but with less severity than MDD. A variation on MDD, bipolar disorder (or, formerly, manic depression) is accompanied by episodic mania [29]. Other types of depression are recognized, e.g., perinatal depression, seasonal affective disorder, and psychotic depression. Depression severities are commonly classed with the aid of the Hamilton Depression Rating Scale (HAM-D) [30].

The mechanisms pertaining to depression are still theorized but generally point to a deficiency. Depressions are explained through the monoamine theory by a lack of three neurotransmitter molecules: serotonin, norephedrine, and dopamine. Alternatively, the more recent neurogenic theory ascribes a deficiency of neurons to cause depression. Medication, psychotherapy, brain stimulation therapy, or a combination thereof can be employed as curatives [31]. Pharmacological treatments aim to either inhibit neurotransmitter re-absorption (e.g., selective serotonin reuptake inhibitors (SSRIs), selective serotonin and noradrenaline reuptake inhibitors (SSNRIs), or tricyclic anti-depressants (TCAs)) or inhibit neurotransmitter-degrading enzymes (monoamine oxidase (MAO)), distinguishable in MAO isoform A (affinitive to serotonin and somewhat norepinephrine) and B (acting strongly on phenylethylamine and benzylamine) [32,33].

Depressive disorders have consistently had a large impact on global DALYs. This burden has increased most recently, exacerbated by the COVID-19 pandemic [34]. Natural officinal remedies have been reported throughout history. For instance, traditional Chinese medicine has employed Panax ginseng root for millennia as a mood enhancer [35,36]. Xu et al. [37] found that ginsenosides, particularly (S)-protopanaxadiol, exhibited strong anti-depressant effects in rats. Similarly, peony extract, a derivative of the Paeonia lactiflora root, was utilized as an anti-depressant in traditional Chinese medicine. Indeed, peony has been shown to exhibit anti-depressant-like effects in stressed rodents [38]. Moreover, the seeds of the Ginkgo biloba have been employed in traditional Chinese medicine for their neuro-protective effects [39]. Curcuma has been incorporated in both traditional Indian and Chinese medicine in an effort to regulate stress and mood disorders [40,41]. Chlorophytum comosum has traditionally been used in traditional medicinal preparations in India, China, and Africa, with the constituent stigmasterol exerting neuroprotective effects [42].
Tea spread from China to Japan as medicine, being later described in the Japanese book Kissa Youjouki as a marvelous medicine preventive for many ailments [43]. Catechins, present in green tea, have experimentally been shown to act as a possible MAO inhibitor in mice [44,45]. Similarly, many other plant molecules/extracts have been found to be psychotropic in experimental models (Table 2).

Table 2. Overview of experimental trials on anti-depressant functions of officinal extracts.

| Plant                  | Organisms                          | Dose                        | Tests                                        | Parameters                                      | Results                                                                 | Reference |
|------------------------|------------------------------------|-----------------------------|----------------------------------------------|------------------------------------------------|--------------------------------------------------------------------------|-----------|
| Ginkgo biloba          | Male BALB/c mice                   | 17-day dose of 5, 10, 20, 40 mg/kg | Forced swimming                            | Immobility period, locomotor activity, and monoamines | Mice exposed to 10 mg/kg/day of G. biloba extract showed a decline of 39% immobility time after forced swimming test. Reduced lipid peroxidation and radicals were associated with the extract. | [46]     |
| Ginkgo biloba          | 136 Elderly humans with depression| Thrice 19.2 mg/day          | Placebo-controlled trial                     | HAM-D * and serum S100B levels                  | Those exposed to G. biloba scored better on the HAM-D and showed lower expression of serum S100B, a brain injury marker. | [47]     |
| Hypericum perforatum   | 20 Male mice (strain BIC57)        | Single dose of 7, 35, 70 mg/kg | Forced swimming and tail suspension         | Immobility period                              | Mice displayed a negative correlation between dose (7, 35, and 70 mg/kg b.m.) of St. John’s Wort extract and immobility time after forced swimming and tail suspension. | [48]     |
| Curcuma longa          | Male Sprague–Dawley rats           | 14-day dose of 2.5, 5, 10 mg/kg | Forced swimming, olfactory bulbectomy, open field, and passive avoidance test | Various levels of monoamines and metabolites, immobility, and behavioral abnormalities | Curcumin administration reversed neurotransmitter deficits induced by olfactory bulbectomy tests in rats. Behavior after olfactory bulbectomy and forced swimming tests was improved. | [41]     |
| Valeriana officinalis  | Albino Laca mice                   | Single- and 14-day admission of 10, 20, 40 mg/kg | Forced swimming                            | Immobility period, locomotor activity, norepinephrine and dopamine levels | Single administration of dichloromethane extracted from valerian significantly inhibited forced swimming-induced immobility in mice. Additionally, sustained administration decreased immobility and increased norepinephrine and dopamine levels. | [49]     |
| Hibiscus tiliaceus     | >40 Male Swiss albino mice         | Single dose of 3, 10, 30 mg/kg | Forced swimming, tail suspension, and elevated plus-maze | Immobility, maze arm entry                     | Methanolic hibiscus flower extracts decreased the period of immobility times. | [50]     |
| Paeonia lactiflora     | 80 Male ICR mice                   | 80 and 160 mg/kg, 7 days    | Forced swimming and tail suspension         | Immobility period and MAO A and B activity     | Peony extracts inhibited MAO A and B activity in mouse brains, significantly reduced immobility times. | [51]     |
### Table 2. Cont.

| Plant                  | Organisms                     | Dose                          | Tests                                      | Parameters                                      | Results                                                                                          | Reference |
|------------------------|-------------------------------|-------------------------------|--------------------------------------------|-------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------|
| *Piper methysticum*    | 60 adult Humans               | 5 doses of 250 mg/day for 3 weeks | Placebo-controlled, double-blind, crossover trial | Hamilton Anxiety Scale, Beck Anxiety Inventory, and Montgomery–Asberg Depression Rating Scale | Aqueous kava extracts reduced all assessed parameters. Additionally, no clinical hepatotoxicity was observed, which has been reason for *P. methysticum*’s withdrawal in some countries. | [52]      |
| *Lavandula angustifolia* | 35 Wistar rats                | Thrice administered 3428 mg/kg | Forced swimming                             | Immobility period                              | Aqueous lavender extracts significantly reduced immobility periods after forced swimming in rats, which was comparable to imipramine (30 mg/kg). | [53]      |
| *Passiflora foetida*   | 30 Male Swiss albino mice     | Single dosage of 100, 200, 300 mg/kg | Forced swimming, tail suspension, and open field | Immobility and locomotor activity               | Methanolic passionflower extracts decreased immobility time in a dose-dependent manner in mice after tail suspension and forced swimming. Results were comparable to fluoxetine (20 mg/kg) and imipramine (15 mg/kg). No significant effects were observed on locomotor activity. | [54]      |

* HAM-D: Hamilton Depression Rating Scale.

### 3. Saffron: Reported Biologically Active Compounds and Their Pharmacology

Saffron herb is host to a plethora of bioactive compounds including carotenoids (crocin, crocins, α-carotene, lycopene, and zeaxanthin), monoterpenoid aldehydes (e.g., picrocrocin and safranal), monoterpenoids (e.g., crocusatines), isophorones, and flavonoids [2,55]. Crocetin and its glycosidic analogues crocin, picrocrocim, and safranal are regarded as the most notable bioactive molecules [56]. A myriad of pharmaco-active functions is attributed to these compounds.

Saffron’s aroma is chiefly attributed to the volatile compound safranal (Figure 1A). Saffanal attenuated oxidative damage induced through cerebral ischemia in rats [57]. Research has found safranal to act on neurological disorders. For instance, safranal proved to be an effective anti-convulsant in mice, whereas crocin did not [58]. Similarly, Hosseinzadeh and Sadeghnia [59] found safranal to be protective against seizures in rats. Other studies on mice have attributed anti-depressant properties to safranal and crocin via the mechanism of inhibiting dopamine, serotonin, and norepinephrine reuptake [60,61].

Crocetin (Figure 1B) and crocins were shown to inhibit in vivo and in vitro angiogenesis, with crocin being more effective [66]. Thus, crocin could possibly be employed to retard abnormal blood vessel growth. Furthermore, crocin has been shown to be anti-carcinogenic. Its mechanisms include the inhibiting synthesis of nucleic acid, enhancement of anti-oxidative systems, apoptosis initiation, and growth hindrance of signaling pathway factors [67]. Conflictingly, Escribano et al. [68] attributed no cytotoxic effect to crocin, whereas the other three compounds did inhibit cell growth.

Crocins, the molecules of subject in this paper, are carotenoids jointly responsible for saffron’s vibrant color. Several of saffron’s curative functions can be related to this group of compounds. It has acute and chronic anti-inflammatory effects. This has been demonstrated in both in vitro cyclooxygenase inhibition assays and in vivo tests with edemas in rodents [69]. Moreover, it has in vivo been shown to relieve cerulein-induced pancreatic inflammation [70]. Furthermore, crocins can alleviate neurological disorders. Georgiadou et al. [71] alleviated...
manually induced schizophrenia-like behavior in rats by administering crocins. Lastly, crocins exhibited anti-depressant activity through neurotransmitter reuptake inhibition. This has been demonstrated in vivo and in vitro [61,72,73]. Notably, crocetins are more readily absorbed than crocins in the gastrointestinal tract of animals [74]. Additionally, crocins are metabolized to crocetins when administered orally [74–76]. However, it has not yet been elucidated how readily crocin is metabolized in humans. Nevertheless, the method of administration must be significant for pharmacokinetics.

Picrocrocin (Figure 1C), a colorless, bitter-tasting compound, shares therapeutic effects with the other three compounds (e.g., anti-carcinogenic) [68]. However, to the best of our knowledge, isolated picrocrocin studies are limited and its role as a neuroprotective agent has not been described yet [77].

4. Role of Saffron Stigma Extract and Crocin in Synaptic Transmission

Crocins are natural carotenoids, commercially obtained from the dried stigma of saffron, occurring with different esterified saccharides on a crocetin backbone, such as trans-crocetin (β-D-glucosyl)-(β-D-gentiobiosyl) ester (named trans-3-Gg), trans-crocetin di-(β-D-glucosyl) ester (named trans-2-gg), trans-crocetin di-(β-D-gentiobiosyl) ester (named trans-4-GG; Figure 1D), trans-crocetin (β-D-gentiobiosyl) ester (named trans-2-G), cis-crocetin (β-D-glucosyl)-(β-D-gentiobiosyl) ester (named cis-3-Gg), and cis-crocetin di-(β-D-gentiobiosyl) ester (named cis-4-GG). Saffron’s brick-red color is generally a result of the glycoside carotenoid structure of crocin [78]. Moreover, the main interest in this herb could be due to its anti-anxiety, anti-convulsant, and hypnotic properties. It is believed that bioactive compounds such as crocin, crocetin, and others are attributed for their anti-oxidant properties, which may partly justify their neuroprotective effects [79].

Several studies have demonstrated that saffron not only inhibits the reuptake of monoamines but also exhibits both N-methyl-D-aspartate (NMDA) receptor antagonism and γ-aminobutyric acid agonism, which seem to be responsible for its anti-depressant-like and anxiolytic effects demonstrated in animal models [80]. It was concluded from the human and animal studies that saffron, mainly crocin, has shown a positive effect in the treatment of mild to moderate depression, which might be possibly due to the interaction of serotonin and the noradrenaline system [81].

According to the studies of various parts of the saffron flower, contractile responses to electrical field stimulation (EFS) in isolated vas deferens in rats were reduced by saffron petal extracts. The contractions of EFS-induced vas deferens were shown to be mediated by noradrenaline and adenosine triphosphate from sympathetic nerves. The ethanolic extract of saffron was noted to show changes in EFS in rats’ isolated vas deferens; however,
the aqueous extract of the saffron was more effective in guinea pig ileum [82]. Saffron and crocin were found to have an inhibitory impact on amyloid beta-peptide fibrillogenesis and a protective action against H2O2-induced toxicity in human neuroblastoma cells in an in vitro study. Saffron (60 mg/kg body weight, i.p.) significantly increased learning and memory in normal and old mice after a week of administration, demonstrating cognitive-enhancing properties [83]. In another study, crocin activity was linked with reactive oxygen species’ production and causing oxidative stress, for instance, by the treatment with 5 and 25 mg/mL of saffron extract; 10 and 50 µM of crocin lowered the neurotoxic effect of glucose in ROS-mediated PC12 cells [84].

Some clinical studies have shown that in a randomized and double-blind study, saffron supplementation statistically improved the mood of subjects compared to the placebo group. For 6 weeks, the administration of saffron extract (30 mg/day) was effective in the treatment of mild to moderate depression based on the HAM-D. These effects were similar to the effects of fluoxetine, which is an anti-depressant known as an SSRI [85,86]. The therapeutic benefits of petals of saffron in the treatment of mild to moderate depression have also been suggested [87]. The efficacy of the co-administration of a hydro-alcoholic extract of saffron (40 or 80 mg) and fluoxetine (30 mg/day) was also investigated in a double-blind, randomized clinical trial for 6 weeks. The results revealed that a dose of saffron of 80 mg plus fluoxetine was more effective to treat mild to moderate depressive disorders than that of saffron of 40 mg and fluoxetine [88].

5. Monoamine-Related Mechanism and Brain Neurotransmitters

All the anti-depressant drugs increase the monoamine concentration in the brain; therefore, it is important to note that depression is defined by the serious condition of brain monoamine reduction [89]. The MAO inhibitory properties of crocin and safranal were evaluated to assess their influence on catecholamine and 5-HT levels in the brain. In particular, crocin was demonstrated to be a non-competitive inhibitor of the human MAO-A and MAO-B in the micromolar range by means of binding to allosteric sites on the enzyme, whereas safranal was inactive toward both isoforms. It is known that MAO-A and MAO-B are two important enzymes that are targets for the treatment of neurodegenerative disorders [90]. Saffron extract co-administered with aluminum induced changes in MAO (A and B) activity and the levels of lipid peroxidation in the whole brain and cerebellum [81].

The emergence of depression is associated with several physiological disturbances in monoaminergic activity, hypothalamus-pituitary-adrenal activity, inflammation, and oxidative and nitrosative stress [91]. Crocin is a group of hydrophilic carotenoids consisting of an esterified monoglycosyl or disaccharide gentiobiose on the dicarboxylic acid crocetin [92]. The possible molecular mechanisms suggest that crocin exerted anti-inflammatory activity in a rabbit osteoarthritic model by inhibiting interleukin 1 beta-induced activation of the nuclear factor-kappa B NF-kB pathway [93]. Furthermore, crocin decreased the mRNA expression of tumor necrosis factor α (TNF-α), IL-1β, IL-6, interferon-γ (IFN-γ), NF-κB, cyclooxygenase-2 (COX-2), and inducible nitric oxide synthase (iNOS) [94].

In another hypothesis of the mechanism, brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin superfamily, which includes growth factors that promote learning and memory by cell survival, differentiation, and death of specific neuronal populations. The epigenetic modulation of BDNF and TRKB genes might contribute to the pathophysiology of depression and related behaviors [93,95]. The anti-depressant-like activity increases the cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB), BDNF, and VGF levels in the hippocampus [96]. Another important family involved in the mechanism belonging to serine/threonine protein kinases is mitogen-activated protein kinases (MAPK), which regulate neuronal activity and synaptic plasticity. Activation of the MAPK cascade requires four sequential events, which include small GTPases (Ras and Rac proto-oncogenes), MAPK kinase kinases (Raf or MEKK), MAPK kinases (MEK), and MAPKs. The activation of the MAPK cascade results in linking the extracellular signals to synaptic responses [96]. The Ras-Raf-MEK1/2 pathway is responsi-
ble for activating extracellular signal-regulated kinase (ERK), which plays a pivotal role in psychiatric disorders including depression and anxiety [97]. High concentrations of crocin significantly reduced p-MEK. Therefore, modulation in the BDNF/CREB/ERK signaling cascade and inhibition through crocin might provide further insights into the importance of behavioral changes during the depression [96].

The expression of pituitary adenylate cyclase-activating polypeptide (PACAP) is inhibited by stress, which results in the inhibition of the phosphorylation of extracellular regulated protein kinases (ERK) and response element binding protein (CREB), and results in the reduction of the translation of synaptic plasticity proteins, which untimely causes depression, as shown in Figure 2A [98]. Saffron crocin can upregulate endogenous PACAP, resulting in the activation of ERK and CREB. This will improve synaptic plasticity and enhance the neuronal survival, as shown in Figure 2B. This mechanism has been reported based on mice and corticosterone cell models.

![Figure 2. Mechanism for the neuroprotective effect of crocin in depression. Stress can cause depression (A), however, saffron crocin can reduce the effect of stress by exhibiting neuroprotection activity (B). PACAP, pituitary adenylate cyclase-activating polypeptide; ERK, extracellular regulated protein kinases; CREB, response element binding protein; cAMP, cyclic adenosine monophosphate; ATP, adenosine triphosphate; AC, adenylyl cyclase [98].](image)

The role of the saffron extract is involved in inhibiting serotonin reuptake in synapses, thereby enhancing its positive effects while combating depression. To date, research suggests that the reuptake inhibition of monoamines, MAO inhibition, NMDA antagonism, and improved brain-derived neurotrophic factor signaling may be mechanistic factors responsible for the treatment of depression from saffron [99].

6. Neurotransmitter Receptors and Possible Targets for Crocin

The cholinergic synapses present in the human central nervous system are responsible for the transmission of critically important brain functions such as memory, learning, attention, etc. [81]. Anti-depressants are reported to function by triggering serotonin, norepinephrine, and dopamine levels in the brain. To confirm this, Ettehadi et al. [100] measured changes in rat brain dopamine, serotonin, norepinephrine, and glutamate concentrations;
after the administration of an aqueous extract of saffron (50, 100, 150, and 250 mg/kg, i.p.), saffron increased brain dopamine concentration in a dose-dependent manner. In addition, the results showed that the aqueous extract of saffron, especially at the dose of 250 mg/kg, increased the production of important neurotransmitters including dopamine and glutamate in rat brain [100]. In fact, it was reported based on animal studies that the possible anti-depressant activity of saffron bioactive compounds (crocin and safranal) could be mainly through inhibiting serotonin reuptake and the inhibition of dopamine and norepinephrine reuptake (Figure 3) [101].

The effects of saffron on conditioning place preference induced by morphine have been reported to be similar to the effect of NMDA receptor antagonists [102]. Therefore, an interaction of saffron and glutamate receptors in the nervous system might be postulated in glutamatergic system. The high calcium permeability through NMDA receptors plays an important role in post-training memory processing by the amygdala and hippocampus parts of the brain [103]. Similarly, the cholinergic system imparting learning and other higher brain functions in the central nervous system have also been mediated by the effect of saffron extract [104,105]. Therefore, there are requirements for more mechanistic-based experiments to study the involvement of saffron extract in cognition and depression.

6.1. Serotonin

It was observed from the abovementioned studies considering a biochemical point of view that crocin from saffron is proven to be able to find a balance with a highly complex mechanism with some of the major neurotransmitters, such as in serotonergic activity, in which each type of neurotransmitter carries specific information and creates a unique set of an individual’s brain chemistry. In addition to that, saffron is reported to modulate the hypothalamus-pituitary-adrenal (HPA) axis and imparts a neuroprotective effect. Saf-
fron is reported to increase the levels of superoxide dismutase, catalase, and glutathione peroxidase, while lowering malondialdehyde levels and inhibiting the lipid peroxidation pathway. Moreover, saffron positively influences brain plasticity in which the ability of neural networks increases through growth and reorganization [106].

6.2. Dopamine

To identify cellular and molecular mechanisms underlying the anti-depressant property of saffron, it is important to measure another important neurotransmitter commonly responsible for creating positive feelings associated with reward or reinforcement activity. In recent studies, saffron was responsible for treating mild to clinical depression. The findings suggested that an aqueous extract of saffron contains an active component that possibly accelerates dopamine and glutamate levels in the brain suffering with depression [100]. Due to the complex anatomy of the brain, it is difficult to investigate whether the dopamine and glutamate are released in the vesicles or in the synaptic space; however, both the aqueous and organic extracts of saffron showed significant results in reducing symptoms of depression.

7. Pharmacological Treatment of Depression with Crocin

Several pharmacological activities have been suggested to be involved in the anti-depressant-like effects (Table 3). In the following section, we discuss these potential treatments and effects of saffron on mild, moderate, and major depression. The emerging interest in herbal medicine for depression will eventually replace the long-standing reliance on synthetic anti-depressants; for example, saffron has gained a reputation to be used as a natural source to fight the symptoms of depression. The studies showed the effect of saffron’s stigma was as effective as chemically derived anti-depressants such as imipramine and fluoxetine in mild to moderate depression [85,86]. Similarly, saffron was equally effective as citalopram in the major depressive disorder with anxious distress [107] and decreased mild to moderate generalized anxiety disorder when compared with sertraline [108].

Table 3. Studies on pharmacological activities relating to anti-depressant-like effects of saffron. BDI, Beck depression inventory; HAE, hydro-alcoholic extract; PCI, percutaneous coronary intervention; CAD, coronary artery disease; HAM-D, Hamilton Depression Rating Scale; PMS: premenstrual syndrome; GAD, generalized anxiety disorder; MMT, methadone maintenance treatment.

| Aim of the Research | Type of Study | No. of Patients | Treatment | Time of Treatment (Weeks) | Results | References |
|---------------------|---------------|----------------|-----------|--------------------------|---------|------------|
| Comparison of saffron and imipramine | Double-blind, randomized trial | 30 | Stigma of saffron, 30 mg/day | 6 | The effect of stigma of saffron was similar to imipramine in the treatment of mild to moderate depression. | [86] |
| Hydro-alcoholic extract of saffron versus fluoxetine | Double-blind, randomized pilot trial | 40 | Stigma of saffron, 30 mg/day | 6 | The effect of stigma of saffron was similar to fluoxetine in the treatment of mild to moderate depression. | [85] |
| Saffron (petal) in the treatment of mild to moderate depression | Double-blind, randomized, and placebo-controlled trial | 40 | Petal of saffron, 30 mg/day | 6 | The outcome on the HAM-D showed that the petal of saffron could produce a significantly better effect than the placebo. | [109] |
Table 3. Cont.

| Aim of the Research                          | Type of Study                        | No. of Patients | Treatment                                      | Time of Treatment (Weeks) | Results                                                                 | References |
|---------------------------------------------|--------------------------------------|-----------------|-----------------------------------------------|---------------------------|------------------------------------------------------------------------|------------|
| Comparison of petal of saffron and fluoxetine | Double-blind, randomized trial       | 40              | Petal of saffron, 15 mg/day (morning and evening) | 8                         | Petal of saffron was found to be similarly effective to fluoxetine in the treatment of mild to moderate depression. | [87,110]    |
| 40 and 80 mg HAE of saffron against fluoxetine | Double-blind, randomized, clinical trial | 60              | Saffron, 40 and 80 mg/day + fluoxetine (30 mg) | 6                         | Effective in treatment of mild to moderate depressive disorders.       | [88,111]    |
| Saffron with fluoxetine in PCI patients      | Double-blind, randomized, clinical trial | 40              | Saffron (30mg/day)                            | 6                         | Effective as fluoxetine (40 mg/day) in improving depressive symptoms of patients who were suffering from major depressive disorder (MDD). | [112]      |
| Saffron and crocin in improving mental and sexual health in CAD patients | Double-blind, placebo-controlled, randomized, clinical trial | 58              | Stigma of saffron, 30 mg/day OR               | 8                         | The outcome of BDI-II scores significantly decreased after 8 weeks of intervention. | [113]      |
| Saffron in the treatment of PMS              | Double-blind, randomized, placebo-controlled trial | 50              | 30 mg, saffron petal during pre-menstrual syndrome | 8                         | The depression measured significantly decreased.                     | [114]      |
| Saffron versus citalopram in the major depressive disorder with anxious distress | Double-blind, controlled, clinical trial | 66              | 30 mg, saffron stigma                          | 6                         | Effective against moderate to major depression.                        | [107]      |
| Saffron as an add-on therapy to sertraline in mild to moderate generalized anxiety disorder | Double-blind, randomized, controlled trial | 40              | 500-mg capsule containing 450 mg of saffron (type not recorded) | 6                         | Decreased mild to moderate generalized anxiety disorder with saffron as well as with sertraline. | [108]      |
| Crocin on depression in subjects with metabolic syndrome | Randomized, double-blind, controlled, clinical trial | 33              | 30 mg, saffron (crocin)                        | 8                         | Decreased depressive symptoms in patients with metabolic syndrome.     | [115]      |
| Aim of the Research                                                                 | Type of Study                                      | No. of Patients | Treatment                                    | Time of Treatment (Weeks) | Results                                                                 | References |
|------------------------------------------------------------------------------------|----------------------------------------------------|----------------|---------------------------------------------|----------------------------|------------------------------------------------------------------------|------------|
| Saffron improved depression and reduced homocysteine level in patients with major depression | Randomized, double-blind study                     | 40             | 30 mg, saffron (stigma) and 20 mg, fluoxetine | 4                         | The BDI score decreased in patients with major depression.            | [116]      |
| Comparison of saffron versus fluoxetine in treatment of mild to moderate post-partum depression | Double-blind, randomized, clinical trial           | 60             | 30 mg, saffron (stigma)                      | 6                         | Significantly decreased mild to moderate depression and post-menopausal hot flashes. | [110]      |
| Affron®, a standardized extract from saffron                                        | Randomised, double-blind, placebo-controlled study| 80             | 14 mg, saffron (stigma)                      | 8                         | Significant reduction in mild to moderate depression.                   | [117]      |
| Saffron in the treatment of anxiety and depression                                     | Double-blind, randomized, and placebo-controlled trial | 60             | 100 mg, saffron (stigma)                      | 12                        | Significant decrease in mild to moderate depression.                   | [118]      |
| Saffron (petal) in the treatment of mild to moderate depression                        | Double-blind, randomized, and placebo-controlled trial | 36             | 30 mg, saffron (stigma) and 40 mg, fluoxetine | 4                         | No significant decrease.                                               | [119]      |
| Effects of saffron on depression and lipid profile                                    | Double-blind comparative study                     | 40             | 30 mg, saffron (petal)                        | 6                         | Decrease in major depression of those who met DSM-IV criteria.          | [109]      |
| Saffron stigma in mothers suffering from mild to moderate post-partum depression     | Double-blind, randomized, placebo-controlled trial | 40             | 30 mg, saffron (type not recorded) and 20 mg, fluoxetine | 4                         | Significant decrease in major depression.                              | [120]      |
| Crocin in major depressive disorder                                                   | Randomized, double-blind, placebo-controlled, pilot clinical trial | 78             | 30 mg, saffron (stigma)                      | 8                         | Significant decrease in mild to moderate depression.                   | [111]      |
| Crocin on psychological parameters in patients under MMT                              | Randomized clinical trial                           | 46             | 30 mg, saffron (crocin) and 20 mg, fluoxetine | 4                         | Significant decrease in major depression.                              | [121]      |
Table 3. Cont.

| Aim of the Research | Type of Study | No. of Patients | Treatment | Time of Treatment (Weeks) | Results | References |
|---------------------|---------------|-----------------|-----------|--------------------------|---------|------------|
| Crocin on psychological parameters in patients under MMT | Randomized, double-blind, placebo-controlled trial | 50 | 30 mg per day, saffron (crocin) | 8 | Improved depression symptoms during methadone maintenance treatment (MMT). | [122] |
| Double-blind, randomized, and placebo-controlled trial | 28 | 150 mg per day, saffron | 6 | Increased serotonin and happiness were further heightened in supplemented group. Anandamide, dopamine, and β-endorphin were significantly increased under supplementation, whereas placebo remained unchanged. | [123] |

Other parts of saffron such as petals proved to be effective on the HAM-D in the treatment of depression [109]. In addition, comparing the results in depressed adult outpatients, it was concluded that the petals of saffron were as effective as the synthetic antidepressant fluoxetine [87]. Even in a randomized, clinical trial, fluoxetine was given with the regulated amount of saffron (40 and 80 mg/day) and showed promising results in the treatment of mild to moderate depression [88]. Saffron significantly decreased the mild to moderate depression in those with post-menopausal hot flashes when compared to fluoxetine [110].

Saffron stigma was shown to reduce mild to moderate post-partum depression in mothers [111]. It was also found to be effective during mild to moderate depression in patients suffering from post-percutaneous coronary intervention [112]. Likewise, an aqueous extract of saffron and its crocin was found to significantly improve mild to moderate depression in patients with coronary artery disease [113]. Additionally, there was significant decrease in the treatment of depression during premenstrual syndrome [114]. Crocin showed lower symptoms of depression in subjects with metabolic syndrome [115]. Saffron comparably improved depression and dysfunction such as reduced homocysteine levels in patients with major depression [116]. Affron®, a standardized extract from saffron, showed a significant reduction in mild to moderate youth anxiety and depressive symptoms [117].

As mentioned in the above studies, the stigma of saffron showed a significant decrease in mild to moderate depression [118] and the petals of saffron were used to improve signs of major depression [109]. When compared to fluoxetine, saffron reduced depression and improved the lipid profile [120]. Crocin also showed a significant decrease in major depression [121]. Similarly, crocin had effects on psychological parameters in patients under methadone maintenance treatment to improve depression-like symptoms [122]. Results revealed that there is huge potential for accepting saffron as an herbal drug for the treatment of mild to moderate depression; however, more research is required for it to be accepted against major depression. Table 3 depicts an overview of studies employing saffron and crocin as anti-depressant.

Crocins have been demonstrated to be potentially applicable as an anti-depressant. However, crocins have been found as poorly bioavailable, with a small percentage permeating the digestive tract [124]. Furthermore, crocins are deglycosylated into crocetin through hydrolysis when orally ingested [56,124,125]. Intra-peritoneal injection does allow unaltered crocins to penetrate the blood–brain barrier [126]. Nevertheless, drug stability and bioavailability should be increased to not hamper the desirable administration route of
oral ingestion. Nanocarriers have been demonstrated to be applicable aids in biological delivery processes [119,123,127]. Various matrices have been shown to increase and retain crocins, increasing delivery and stability (Table 4). The exploitation of nanomaterials poses a promising route. However, the efficacy of gastrointestinal tract and blood–brain barrier permeation and crocin hydrolysis remains unspecified in most cases.

Table 4. Effect of experimental drug delivery systems on stability, loading, and bioavailability of crocin, as reported in literature.

| Matrix                                      | Results                                                                                                                                                                                                 | Reference |
|---------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Chitosan-alginate nanoparticles             | Highest crocin loading achieved at pH 1.2 with a biphasic release in simulated gastric fluids. The loaded nanoparticles were equivalent in DPPH free radical scavenging and ferric-reducing ability of plasma as free crocin and exhibited an anti-cancer effect. | [128]     |
| Maltodextrin nanoencapsulates               | Nanoencapsulated crocin was more stable at simulated gastrointestinal conditions. While encapsulation increased bioaccessibility (from 61% to 72%), the combination of caffeic acid with encapsulation increased the bioaccessibility to almost 80%. | [129]     |
| Maltodextrin/pectin/whey protein concentrate nanoencapsulates | Combinations of whey protein concentrate and pectin yielded the highest crocin encapsulation efficiencies, exceeding 95%. Thus, minimal amounts of crocins were exposed at the particles' surfaces. Furthermore, an improved stability against stressors was suggested. | [130]     |
| Chitosan-gum arabic nanoencapsulates         | Crocin was encapsulated with an efficiency of 29 to 52%. The release profiles showed an oscillatory relationship with time at pH 1 and 2. This oscillatory relation was suggested to be a result of rapid degradation of released crocin. | [131]     |
| Cholesterol-Tween 40 nanoniosomes           | Encapsulation efficiency was 46%, and 61% of crocin was released after 6 h in mice. Intra-arterially injected crocin-laden niosomes decreased ischemic indicator molecules in rats and mitigated I/R tissue damages. | [132]     |
| Bacterial nanocellulose membrane            | The nanocellulose membrane exhibited a stable and prolonged transdermal release through mice skin in a Franz diffusion cell. | [133]     |
| Chitosan-alginate                           | An encapsulation efficiency of 92% was attained. The resulting nanoparticles stabilized crocin degradation at pH 2, enhanced bioavailability, and showed a pH-mediated release. | [134]     |
| Solid lipid nanoparticles                   | Increased stability, high encapsulation efficiency. | [135]     |
| Selenium nanoparticles                      | Crocin release rate was pH dependant, with 91% released after 48 h at pH 5.3, whereas just a mere 35% was released at pH 7.4 during the same time. The administration of loaded nanoparticles resulted in enhanced cytotoxicity in lung cancer cells and inhibited tumor growth in a mice model. | [136]     |
| Polylactic-co-glycolic acid nanoparticles   | Entrapment efficiency reached 59%, and 78% of crocin was released after 24 h at pH 7.4, sustaining release throughout 48 h. Release was increased at pH 6.5 to 84% after 24 h. | [137]     |

8. Conclusions and Future Perspectives

For ages, people have preferred the dried stigma of *Crocus sativus* (saffron) for medicinal and nutritional purposes in different parts of the world, mainly in Central Asia, Iran, China, India, Turkey, Algeria, and Europe. The most active biological compounds include crocetin, crocin, picrocrocin, and safranal, which are responsible for color, taste, and fragrance, respectively. These play a pivotal role in the central nervous system associated with anxiety and depression. These bioactive compounds are also neuroprotective and anxiolytic and can benefit learning and memory impairments. The most popular anti-depressants that are prescribed by physicians are tricyclic anti-depressants (TCAs), selective serotonin reup-
take inhibitors (SSRIs), and selective serotonin noradrenaline reuptake inhibitors (SSNRIs). The primary mechanism works by enhancing serotonin, a special neurotransmitter.

The high cost of saffron is due to labor-intensive production, which initially requires handpicked stigmas for saffron. These precious stigmas contain all the bioactive compounds that are responsible for its medicinal properties. This existing evidence suggests that saffron has a potential to be used efficaciously to alleviate the symptoms of depression in different conditions from pre-menstrual to post-partum. On the contrary, this statement has to be supported by more clinical evidence and large-scale trials among these areas of study to address methodological limitations and a lack of global diversity in clinical recommendations. A wider perspective can open avenues for a detailed mechanistic approach, proper dosage, more bioactive composition, and the long-term safety in the herbal industry. However, natural compounds have major challenges such as low bioavailability. Furthermore, natural compounds are generally rapidly metabolized and have the ability to cross the blood–brain barrier. Perhaps these challenges could be overcome with the development of nanocarriers that are site specific and target the diseased subset of neurons instead of affecting healthy neurons. The targeted delivery of natural compounds to the affected part of the brain can result in designing a system that includes reduced side effects and the controlled release of particular drugs as well as a higher bioavailability of a drug at a particular site. Therefore, brain delivery of natural inhibitors through a nanocarrier-based approach is futuristic, will contribute to potential CNS therapies, and will allow a novel strategy for saffron in therapeutic applications.

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