Anti-Depressant Properties of Crocin Molecules in Saffron

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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 research. 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 in the treatment of depression disorders. Saffron and crocins propose a natural solution to combat depressive disorders. However, some hurdles, such as stability and delivery, need to be overcome.

Crocus sativus saffron crocin natural anti-depressants traditional medicine

1. Saffron: Reported Biologically Active Compounds and Their Pharmacology

Saffron herb is host to a plethora of bioactive compounds including carotenoids (crocetin, crocins, α-carotene, lycopene, and zeaxanthin), monoterpene aldehydes (e.g., picrocrocin and safranal), monoterpenoids (e.g., crocusatines), isophorones, and flavonoids [1][2]. Crocetin and its glycosidic analogues crocin, picrocrocin, and safranal are regarded as the most notable bioactive molecules [3]. A myriad of pharmaco-active functions is attributed to these compounds.

Saffron's aroma is chiefly attributed to the volatile compound safranal (**Figure 1**A). Safranal attenuated oxidative damage induced through cerebral ischemia in rats [4]. 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 [5]. Similarly, Hosseinzadeh and Sadeghnia [6] 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 [7][8].

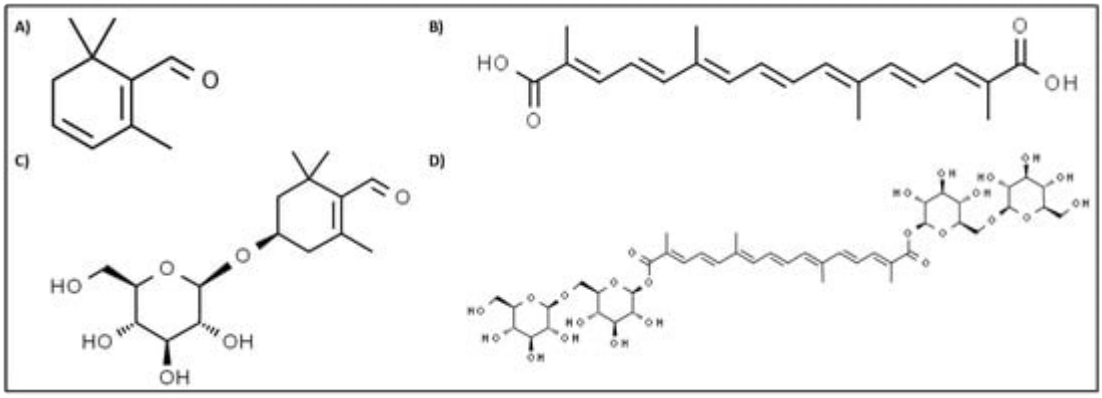

Figure 1. Structural formulas of saffron constituents safranal (**A**) [8], trans-crocetin (**B**) [9], picrocrocin (**C**) [10], and trans-crocetin digentiobiose ester (**D**) [11], one of crocin's many forms [12].

Crocetin (**Figure 1**B) and crocins were shown to inhibit in vivo and in vitro angiogenesis, with crocetin being more effective [13]. Thus, crocetin could possibly be employed to retard abnormal blood vessel growth. Furthermore, crocetin 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 [14]. Conflictingly, Escribano et al. [15] attributed no cytotoxic effect to crocetin, whereas the other three compounds did inhibit cell growth.

Crocins, the molecules of subject in this research, 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 [16]. Moreover, it has in vivo been shown to relieve cerulein-induced pancreatic inflammation [17]. Furthermore, crocins can alleviate neurological disorders. Georgiadou et al. [18] 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 [8][19][20]. Notably, crocetins are more readily absorbed than crocins in the gastrointestinal tract of animals [21]. Additionally, crocins are metabolized to crocetins when administered orally [21][22][23]. 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 1**C), a colorless, bitter-tasting compound, shares therapeutic effects with the other three compounds (e.g., anti-carcinogenic) [15]. However, to the best of the researchers' knowledge, isolated picrocrocin studies are limited and its role as a neuroprotective agent has not been described yet [24].

2. 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 1**D), *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 [25]. 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 [26].

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 [27]. 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 [28].

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 [29]. Saffron and crocin were found to have an inhibitory impact on amyloid beta-peptide fibrillogenesis and a protective action against H_2O_2-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 [30]. 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 [31].

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 [32][33]. The therapeutic benefits of petals of saffron in the treatment of mild to moderate depression have also been suggested [34]. 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 [35].

3. Pharmacological Treatment of Depression with Crocin

Several pharmacological activities have been suggested to be involved in the anti-depressant-like effects (**Table 1**). 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 [32][33]. Similarly, saffron was equally effective as citalopram in the major depressive disorder with anxious distress [36] and decreased mild to moderate generalized anxiety disorder when compared with sertraline [37].

Table 1. 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.	[33]
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.	[32]
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.	[38]
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.	[34][39]
40 and 80 mg HAE of saffron	Double-blind, randomized,	60	Saffron, 40 and 80	6	Effective in treatment of mild to	[35][40]

Aim of the Research	Type of Study	No. of Patients	Treatment	Time of Treatment (Weeks)	Results	References
against fluoxetine	clinical trial		mg/day + fluoxetine (30 mg)		moderate depressive disorders.	
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).	[41]
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.	[42]
Saffron in the treatment of PMS	Double-blind, randomized, and placebo-controlled trial	50	30 mg, saffron petal during pre-menstrual syndrome	8	The depression measured significantly decreased.	[43]
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.	[36]
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.	[37]
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.	[44]

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.	[45]
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.	[39]
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.	[46]
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.	[47]
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.	[48]
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.	[38]
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.	[49]

Aim of the Research	Type of Study	No. of Patients	Treatment	Time of Treatment (Weeks)	Results	References
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.	[40]
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.	[50]
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).	[51]
	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 suplementeation, whereas placebo remained unchanged.	[52]

Other parts of saffron such as petals proved to be effective on the HAM-D in the treatment of depression [38]. 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 [34]. 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 [35]. Saffron significantly decreased the mild to moderate depression in those with post-menopausal hot flashes when compared to fluoxetine [39].

Saffron stigma was shown to reduce mild to moderate post-partum depression in mothers [40]. It was also found to be effective during mild to moderate depression in patients suffering from post-percutaneous coronary intervention [41]. Likewise, an aqueous extract of saffron and its crocin was found to significantly improve mild to moderate

depression in patients with coronary artery disease [42]. Additionally, there was significant decrease in the treatment of depression during premenstrual syndrome [43]. Crocin showed lower symptoms of depression in subjects with metabolic syndrome [44]. Saffron comparably improved depression and dysfunction such as reduced homocysteine levels in patients with major depression [45]. Affron®, a standardized extract from saffron, showed a significant reduction in mild to moderate youth anxiety and depressive symptoms [46].

As mentioned in the above studies, the stigma of saffron showed a significant decrease in mild to moderate depression [47] and the petals of saffron were used to improve signs of major depression [38]. When compared to fluoxetine, saffron reduced depression and improved the lipid profile [49]. Crocin also showed a significant decrease in major depression [50]. Similarly, crocin had effects on psychological parameters in patients under methadone maintenance treatment to improve depression-like symptoms [51]. 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 1** depicts an overview of studies employing saffron and crocin as an 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 [53]. Furthermore, crocins are deglycosylatized into crocetin through hydrolysis when orally ingested [3][53][54]. Intra-peritoneal injection does allow unaltered crocins to penetrate the blood–brain barrier [55]. 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 [48][52][56]. Various matrices have been shown to increase and retain crocins, increasing delivery and stability (**Table 2**). 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 2. 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.	[57]
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%.	[58]
Maltodextrin/pectin/whey protein concentrate	Combinations of whey protein concentrate and pectin yielded the highest crocin encapsulation efficiencies, exceeding 95%.	[59]

Matrix	Results	Reference
nanoencapsulates	Thus, minimal amounts of crocins were exposed at the particles' surfaces. Furthermore, an improved stability against stressors was suggested.	
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.	[60]
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.	[61]
Bacterial nanocellulose membrane	The nanocellulose membrane exhibited a stable and prolonged transdermal release through mice skin in a Franz diffusion cell.	[62]
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.	[63]
Solid lipid nanoparticles	Increased stability, high encapsulation efficiency.	[64]
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.	[65]
Poly(lactic-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.	[66]

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