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Review

Clinical Perspective on The Effects of *Crocus sativus* in Depression and Attention Deficit Hyperactivity Disorder and Sleep Quality

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Abstract

Crocus sativus L. (saffron) is a valuable plant used as a spice and for therapeutic purposes in many cultures, especially in the Middle East and the Mediterranean, since ancient times. The therapeutic effects of saffron are based on the bioactive compounds found in its stigma—most notably crocin, crocetin, safranal, and picrocrocin. These compounds have been shown to have antioxidant, anti-inflammatory, neuroprotective, and antidepressant properties in various *in vitro, in vivo*, and clinical studies. Recent studies have begun to examine the effects of saffron more systematically, especially on neuropsychiatric disorders such as depression and attention deficit hyperactivity disorder. It has been reported that saffron extracts are effective at a level comparable to some antidepressants in cases of mild to moderate depression; they may also help reduce attention and behavioral problems in attention deficit hyperactivity disorder. This review summarizes the phytochemical structure of saffron, compiles preclinical and clinical data on its antidepressant and attention-modulating effects, and discusses potential areas of application for future research.

Keywords: Attention deficit hyperactivity disorder, *Crocus sativus*, depression, saffron, sleep quality

1. Introduction

The *Crocus* genus is represented by 235 species worldwide, 103 of which grow in Türkiye (1-7). *Crocus sativus* L. (*C. Sativus*), which has a high economic value and is in high demand in the world, is a plant belonging to the Iridaceae family, known as "Saffron" in Turkish, and is grown in Asia (Iran, Azerbaijan, India, Pakistan, and China), Europe (Greece, Italy, France, and Spain), North Africa (Morocco and Egypt), the Middle East (Israel), New Zealand, and Türkiye. The word "zaferan," which is of Arabic origin and means yellow, is used in various languages with minor alterations. For instance, it appears as "safran" in German, Turkish, and French; "saffron" in English; "shafran" in Russian; "zafferano" in Italian; and "zafora" in Greek, all referring to this plant. "Saffron," scientifically known as *C. sativus*, is referred to Kürkum in Middle Eastern agriculture (8).

C. sativus, an agricultural product generally grown in continental and temperate climates, can grow in temperatures between – 10 and 35°C, and it has been reported that it can also withstand high temperatures. The pharmaceutical, dye, cosmetic, and food industries use the plant's stigmas, known

as saffron. The high-profit potential of the saffron trade has led countries other than traditional producer countries to show interest in saffron production. Iran, which accounts for more than 90% of global production, is today the world's largest saffron producer, followed by Spain, Afghanistan, Portugal, and France. The countries that import the most saffron are the USA, the United Arab Emirates, and European countries (9).

C. sativus is the most prominent species of the *Crocus* genus regarding traditional uses and is noted for its widespread use in folk medicine across Egypt, Greece, India, Persia, and Rome. In Islamic traditional medicine and Ayurvedic medicine, saffron is widely used for its aphrodisiac effect, and it has been reported to be used as a nerve tonic, emmenagogue, appetite stimulant, and stimulant, as well as to treat dysmenorrhea, stomach ulcers, and premature ejaculation. In traditional Chinese medicine, the topical application of saffron stigma is recommended in treating asthma, whooping cough, and inflammation. Saffron is used for insomnia, migraines, and metabolism in Iraq; for toothache in Spain, and for indigestion and as a sedative in Italy (10).

Saffron was used in ancient Egypt to strengthen the stomach and liver and to cure digestive system diseases. In ancient Rome, saffron was used for lung and eye inflammation, liver disorders, and to stop coughs. In Turkish Islamic medicine, saffron is known to enhance eyesight, aid digestion, strengthen the heart, alleviate headaches, improve memory, regulate sleep, and soothe the nervous system (11). Additionally, it is a key ingredient in mesir paste, which has been produced in Anatolia since 1539 and is utilized in the treatment of various diseases, particularly infertility (12).

Many studies have been investigated the biological activities and phytochemical profile of *C. sativus*, including its leaves, tepals, petals, stigmas, and bulbs. This review examines the phytochemical content of its stigmas, commonly known as saffron, as well as its effects on anxiety and attention deficit-hyperactivity disorders (ADHD), which have been the focus of more recent research.

2. Botanical Characteristics of *C. sativus*

C. sativus var. *officinalis* L. Species Plantarum 1:36 (1753)

Synonyms

C. officinalis var. *sativus* Huds (1778), *C. sativus* var. *casbmiruanus* Royle (1836), Geanthus autumnalis Raf., Specchio Sci. 1: 116 (1814), *C. sativus* var. *cashmerianus* Royle, Ill. Bot. Himal. Mts. 1: t. 90, f. 1 (1834), *C. orsinii* Parl., Fl. Ital. 3(2): 238 (1860), *C. sativus* var. *orsinii* (Parl.) Maw, Gard. Chron., n.s., 11: 234 (1879), *C. autumnalis* Sm. in Engl. Bot.: t. 343 (1796), nom. Illeg, *C. officinalis* (L.) Honck. in Syn. Pl. Germ. 1: 273 (1792), *C. orsinii* Parl. in Fl. Ital. 3: 238 (1860), *C. pendulus* Stokes in Bot. Comm. 1: 209 (1830), *C. sativus* var. *cashmerianus* Royle in Ill. Bot. Himal. Mts. 1: t. 90, f. 1 (1834), *C. sativus* var. *orsinii* (Parl.) Maw in Gard. Chron., n.s., 11: 234 (1879), *C. sativus* subsp. *orsinii* (Parl.) K.Richt. in Pl. Eur. 1: 248 (1890), *C. setifolius* Stokes in Bot. Mat. Med. 1: 104 (1812), *Geanthus autumnalis* Raf. in Specchio Sci. 1: 116 (1814), *Safran officinarum* Medik. in Hist. & Commentat. Acad. Elect. Sci. Theod.-Palat. 6: 473 (1790) (13, 14).

Cormus is large, measuring up to 32 mm in diameter, and flat-based; the tunic is thin and reticulate fibrous, with no ring present. There are 4 or 5 cataphylls. The leaves number between 5 and 11, reaching up to 2 mm in width, with margins that are ciliated and have a keel. The perigon tube is purple, and the floral segments are obtuse, measuring 50 × 20 mm, bright lilac-purple, dark-veined, and featuring a dark spot near the base; the throat is pubescent, ranging from whitish to purple. The filaments measure 7-11 mm in length, are bare, and purplish; the anthers are 5-20 mm long, yellow, with indistinct connective tissue. The style is located at the base or middle of the anthers and is divided into three long, dark red, soft, hanging branches, each measuring 25-32 mm. The capsule and seed are not present (15).

3. Phytochemical Profile of *C. sativus*

Findings from phytochemical studies conducted to date have shown that saffron contains primary

metabolites such as carbohydrates, minerals, fats, vitamins, amino acids, and proteins, and secondary metabolites such as carotenoids, monoterpenes, and flavonoids. The composition of saffron stigmas consists of 14-16% water, 11-13% nitrogenous compounds (alkaloids), 12-15% carbohydrates (mucilage, starch, and gums), 41-44% nitrogen-free soluble compounds (saponins, anthocyanins, flavonoids), 0.6-0.9% volatile oil, 4-5% cellulose, and 4-6% minerals. Riboflavin (56-138 µg/g) and thiamine (0.7-4 µg/g) are also found in saffron. Additionally, the presence of 150 volatile and aromatic compounds (β-isophorone, linalool, α-isophorone, α, β-dihydro-β-ionone etc.) in saffron stigmas was determined by GC-MS. The compounds responsible for the characteristic color (crocin), smell (safranal), and taste (picrocrocin) of saffron have been identified (Fig 1). Crocin is a hydrophilic carotenoid that, when hydrolyzed, yields gentiobiose and crocetin. Safranal is produced through the enzymatic reaction of picrosin, which is a degradation product of zeaxanthin, releasing glucose (16, 17).

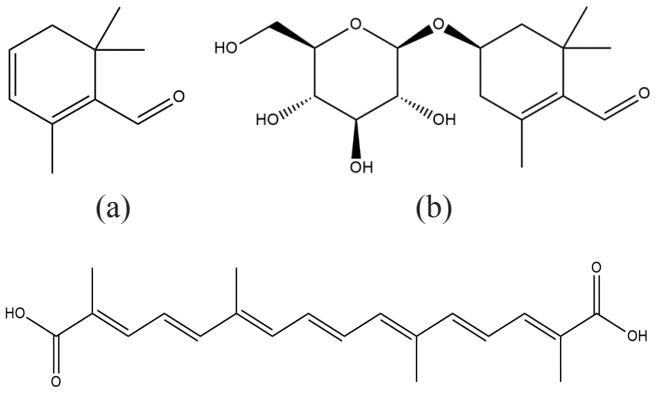

Figure 1. Formulas of (a) safranal, (b) picrocrocin, and (c) crocetin.

The stigmas also contain flavonoids such as kaempferol-3-sophoroside, kaempferol-3-sophoroside-7-glucoside, kaempferol-3,7,4′-triglucoside, kaempferol tetrahexoside, kaempferol-3-dihexoside, isorhamnetin-3-*O*-glucoside, sophoraflavonoloside, quercetin, rutin, quercetin, hesperidin, luteolin, and naringin and coumarins (osthol, isopimpinellin). The stigmas have also been reported to contain some a-hydroxy acids (lactic acid, malic acid, and glycolic acid), fatty esters (methyl arachidate, methyl oleate, methyl palmitate, and methyl stearate), and gallic acid (10,17).

4. Biological Activities of *C. sativus*

To date, numerous studies have been conducted to evaluate the biological activity of extracts obtained from the petals and stigmas of *C. sativus* and the compounds isolated from them (crocin, safranal, and crocetin). These studies are listed below (16,18,19);

- Anticancer/antitumor activity
- Antidepressant and anxiolytic activities
- Antidiabetic activity
- Antigenototoxic and cytotoxic effects
- Antihypertensive activity
- Antinociceptive and anti-inflammatory effects
- Antioxidant activity
- Antitussive activity
- Aphrodisiac effects
- Effects on Alzheimers and Parkinson diseases
- Effects on cardiovascular system
- Effects on gastrointestinal system
- Effects on memory and learning
- Effects on ocular blood flow and retinal function
- Effects on respiratory system
- Effects on urinary system

5. Clinical Studies

5.1. Effects of *C. sativus* in Depression

In the study conducted by Akhondzadeh et al. on 30 patients diagnosed with major depression according to the DSM IV scale, the effects of saffron extract were compared with imipramine. In a 6-week, double-blind, randomized, single-center study, patients were given 30 mg/day saffron extract (Group I) and 100 mg/day imipramine (Group II). Each saffron capsule contains 10 mg of dried 80% ethanol stigma extract. Stigma extract was found to be effective in improving symptoms of mild to

moderate depression, similar to imipramine at a dose of 30 mg/day (F = 2.91, d.f. = 1, p = 0.09). Even anticholinergic side effects (dry mouth and sedation) were more common in the imipramine group (20).

In a six-week double-blind, placebo-controlled, randomized study conducted in Iran in 2005, 40 adult outpatients diagnosed with depression according to DSM IV scale were evaluated with the Hamilton depression rating scale to evaluate the efficacy of saffron stigmas in the treatment of mild to moderate depression. For this purpose, 20 patients were given 30 mg/day saffron capsules every day. The other 20 patients were assigned to the placebo group. At the end of 6 weeks, it was concluded that the improvement in the mood of the saffron group patients was significantly better than the placebo group patients according to the Hamilton depression rating scale. Saffron capsules, which have a low side effect profile, have been reported to be effective in the treatment of mild to moderate depression (21).

In a 6-week double-blind, randomized study, Noorbala et al. investigated the efficacy of standardized saffron stigma aqueous-ethanolic extract on the basis of safranal in the treatment of mild to moderate depression. For this purpose, 19 patients diagnosed with depression according to DSM-IV criteria received capsules containing standardized saffron stigma extract (15 mg) twice a day. To evaluate the effectiveness of the extract, 19 other patients were given 20 mg of fluoxetine per day. In the study evaluating symptoms according to the Hamilton Rating Scale for Depression (HAM-D 17-item), saffron stigma extracts were found to be similarly effective to fluoxetine in the treatment of mild to moderate depression. It was concluded that no significant differences were found in the side effects between the two patient groups. The findings of the study showed that saffron stigma extract may be effective in the treatment of mild to moderate depression, however, these studies should be continued on more subjects (22).

Akhondzadeh Basti et al. studied the efficacy of capsules prepared from *C. sativus* petals in an 8-week pilot, double-blind, randomized clinical trial in 40 patients diagnosed with depression according to DSM-IV criteria. Fluoxetine, a selective serotonin reuptake inhibitor, was utilized for efficacy comparison. Twenty patients were given the petal capsules (15 mg) twice daily. Fluoxetine group patients (n=20) received 10 mg of the drug twice daily, morning and evening. According to the Hamilton Depression Rating Scale, at the end of the treatment, it was found that the petal capsules showed an effect profile similar to fluoxetine in mild to moderate depression. The remission rate for both treatments was determined to be 25%, and there was no notable difference between the two groups regarding side effects (23).

Hausenblas et al. conducted a meta-analysis of randomized controlled trials to evaluate the efficacy of saffron supplements in patients with major depression. The researchers searched the Allied and Complementary Medicine Database, Cumulative Index to Nursing and Related Health Literature, Cochrane Library, EMBASE, MEDLINE, PubMed, and Web of Science databases. Five randomized controlled trials that met the study criteria were included in the meta-analysis, and the quality of the data was assessed using the Jadad score. In studies comparing the effects of imipramine and fluoxetine on depressive symptoms, no difference was found between saffron and these two drugs in terms of their ameliorative effects on depressive symptoms. Researchers emphasized that more controlled, long-term studies with a larger number of subjects should be designed to determine the effectiveness, mechanism of action, and safety of saffron in the treatment of major depression (24).

It is known that 50% of coronary artery patients experience some depressive symptoms, and some are diagnosed with major depression. Shahmansouri et al. evaluated the efficacy of saffron extract (capsule containing 15 mg saffron extract) against fluoxetine in a double-blind, parallel, randomized study on 40 patients diagnosed with mild to moderate depression who underwent percutaneous coronary intervention. In the 6-week study, patients in the positive control group were given 40 mg of fluoxetine per day, while patients in the saffron group were given capsules containing a standardized extract at a dose of 30 mg per day. The Hamilton

Depression Rating Scale (HDRS) was used to assess the efficacy of the treatments administered at 3 and 6 weeks. Despite the relatively small sample size and short observation period, there was no significant difference in the reduction of HDRS scores between the two groups at the beginning and end of treatment. There were also no significant differences between the two groups in terms of adverse reactions (25).

Talaei et al. studied the effect of crocin tablets in a randomized, double-blind, placebo-controlled, pilot clinical trial in 40 patients with major depression (age range 24 to 50 years) for 4 weeks. Patients in the crocin group (n=20) received crocin tablets (30 mg/day) along with a selective serotonin reuptake inhibitor (SSRI) (fluoxetine (20 mg/day), sertraline (50 mg/day), or citalopram (20 mg/day)). On the other hand, patients in the placebo group (n=20) received the same SSRI treatment along with a placebo (two tablets per day).Here, Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), General Health Questionnaire (GHQ), Mood Disorder Questionnaire (MDQ), and Side Effect Assessment Questionnaire were used to evaluate the results. Compared with the placebo group, significant improvements were found in BDI, BAI, and GHQ in crocin group patients, and it was concluded that crocin tablets increased the effects of SSRIs in patients with mild to moderate depression ($p< 0.0001$). As a result, it has been reported that crocin can be used as a therapeutic adjuvant in depression because it does not cause significant side effects (26).

Sahraian et al. tested saffron extract against fluoxetine in a randomized, double-blind, placebo-controlled clinical trial in 30 patients diagnosed with major depression according to DSM-IV criteria. In this study, the treatment group received one capsule containing 30 mg of saffron extract along with 20 mg of fluoxetine each day. In contrast, the placebo group received only a placebo and 20 mg of fluoxetine. After four weeks of treatment, improvements in symptoms were evaluated using the Beck Depression Scale, and no significant difference in symptom improvement was observed between the two groups. However, the placebo group reported a higher incidence of side effects, such as headaches, abdominal discomfort, and nausea, compared to the treatment group. Researchers pointed out that different doses need to be tested, more patients need to be included, and longer-term clinical studies need to be conducted to determine the effectiveness of saffron better (27).

The effects of capsules containing 50 mg of dried saffron stigma were evaluated in a double-blind, placebo-controlled clinical trial conducted for 12 weeks in sixty patients with anxiety and depression, compared with placebo. BDI and BAI questionnaires were used to examine the efficacy of saffron capsules, and subjects were asked to answer these questionnaires at baseline and 6 and 12 weeks after starting the medication. It was determined that saffron stigma capsules caused improvements in BDI and BAI scores after 12 weeks of treatment, while very few side effects were observed (28).

In a randomized, double-blind, and placebo-controlled study to determine the effect of saffron on the anxiety and sleep quality of diabetic patients, the Spielberger Anxiety Inventory and also the Pittsburgh Sleep Quality Index were used to evaluate the efficacy. For this purpose, fifty diabetic patients were divided into two groups of equal numbers. The intervention group was given a capsule containing 300 mg of saffron, while the control group patients received a placebo. In the one-week clinical study, a significant difference was observed in the anxiety and sleep quality of the intervention group patients when compared to the beginning of the treatment ($p = 0.001$). There were no significant differences in anxiety and sleep quality before and after treatment in the placebo group ($p = 0.001$). The study asserted that saffron can be used as an adjuvant treatment in reducing anxiety and improving sleep quality in diabetic patients (29).

Jafarnia et al. conducted a placebo-controlled, double-blind, randomized controlled trial to evaluate the efficacy of saffron as an adjuvant in 40 patients diagnosed with anxiety according to DSM IV and receiving sertraline treatment (50 mg/day). The treatment group received sertraline and 450 mg/day saffron capsules, while the other group received both sertraline and placebo capsules for six weeks. The results were evaluated with the

Hamilton Anxiety Rating Scale (HAM-A). At the end of the 6th week, the total HAM-A scores of the saffron-treated patients were significantly lower than those of the placebo (2.95 vs. 5.05; p value = 0.005). The findings suggest that the use of saffron as an adjuvant to sertraline treatment may reduce anxiety symptoms, but clinical studies with a larger number of participants and a longer duration are needed to reach a definitive conclusion (30).

Lopresti et al. studied the effects of standardized saffron extract on mild to moderate anxiety and depressive symptoms in a randomized, double-blind, placebo-controlled study of 68 adolescents (ages 12-16) over eight weeks. Youth and parent versions of the Revised Child Anxiety and Depression Scale (RCADS) were used to assess symptom improvements. Each capsule used in the study consisted of a standardized extract (affron®) containing 14 mg of Lepticrosalides® with a concentration exceeding 3.5%. The Lepticrosalides® contained safranal and crocin isomers derived from the stigmas of the plant. These capsules were administered to adolescents twice daily. After eight weeks, adolescents reported that standardized saffron extract improved overall internalizing symptoms (p=0.049), separation anxiety (p=0.003), social phobia (p=0.023), and depression (p=0.016) more than placebo. However, parents did not report improvements in these symptoms as positively as adolescents (31).

Toth et al. conducted a meta-analysis of randomized and controlled clinical trials to assess the efficacy of saffron in treating mild to moderate depression. For this purpose, PubMed, Embase, Cochrane Central Register of Controlled Trials, and Web of Science databases were searched, and the RevMan statistical program was used. Hedges' g was used to calculate effect sizes, while both Cochran's Q test and Higgins' I^2 indicator were used for heterogeneity, and the risk of bias was assessed using the Cochrane Collaboration tool. Nine out of eleven selected randomized trials were reviewed for statistical analysis and concluded that saffron has a significant effect on the severity of depression. Available data support the idea that saffron is significantly more effective than placebo (g = 0.891; 95% CI: 0.369–1.412, p = 0.001), and is competitive with the antidepressant drugs (fluoxetine, citalopram, and imipramine) tested (g = − 0.246; 95% CI:-0.495–0.004, p = 0.053) (32).

In the meta-analysis to evaluate the efficacy of saffron in depression and anxiety, literature was accessed using PRISMA guidelines, and twenty-three clinical studies were found to meet the criteria. Most of the twenty-three studies utilized saffron at a dose of 30 mg per day (n = 19/23). Some studies employed saffron stigma (n = 10), while others used saffron petals (n = 4). Three studies investigated crocin, and the remaining six studies examined saffron powder. In the evaluated studies, findings related to a total of 1237 participants were examined. Treatment durations varied from 4 to 12 weeks, and the studies assessed efficacy by comparing saffron monotherapy to saffron combined with either a placebo or antidepressant medications such as fluoxetine, imipramine, and citalopram. Meta-analysis results indicated that saffron caused a significant improvement compared to placebo for depressive symptoms ($p < 0.001$) and anxiety symptoms ($p < 0.006$) and can be used as an adjuvant to conventional drug therapy in the treatment of depression (33).

Khaksarin et al. conducted a meta-analysis of clinical studies on the efficacy of saffron versus fluoxetine in treating depression. Articles published on this topic up to May 2018 were retrieved from various databases, including the Cochrane Library, Scopus, PubMed/MEDLINE, the Centre for Reviews and Dissemination, EMBASE, and ISI/Web of Science. As a result of the initial literature searches, 157 studies were reached, only 8 of which were found to meet the selection criteria, and data from a total of 368 participants were evaluated. In the studies whose quality was approved according to the Cochrane checklist, it was determined that the participants were given fluoxetine in the dose range of 20-40 mg/day and saffron capsules in the dose range of 30-50 mg/day. Meta-analysis findings demonstrated that saffron was well comparable to fluoxetine and placebo in the treatment of depression (34).

Also, a meta-analysis published in 2023 evaluated the overall effects of saffron on cognition,

depression, anxiety, sleep disorders, attention-deficit/hyperactivity disorder, and obsessive-compulsive disorder. To achieve this, the PubMed/Medline, Web of Science, and Clinical Trials databases were searched for randomized controlled trials published on this topic up to June 2023. RevMan and STATA software programs were utilized for the meta-analysis of forty-six randomized controlled trials involving participants who were either healthy or suffering from various diseases, including neurological and psychiatric disorders. These participants were treated with saffron or its extracts, either alone or in combination with conventional medications, for durations ranging from 4 to 48 weeks. Out of forty-six clinical studies, seven were focused on cognitive disorders, thirty-two on depression, fourteen on anxiety, nine on sleep disorders, four on ADHD, and two on obsessive-compulsive disorders. Cochrane guidelines were used to assess the risk of bias. The findings indicated that the overall effect size of saffron in enhancing cognitive disorders and alleviating depression was 4.26 (95% CI: 5.76, 2.77). In terms of anxiety, the effect size was 3.75 (95% CI: 5.83, 1.67), and for sleep disorders, it was 1.91 (95% CI: 2.88, 0.93). Saffron was also found to be more effective than placebo across all studies. Meta-analysis has highlighted that saffron may be as effective as conventional medications in treating ADHD and obsessive-compulsive disorders, it may also offer preventive effects against neurological and psychiatric disorders, and has a low side effect profile (35).

5.2. Effects of *C. sativus* in ADHD

ADHD is one of the most prevalent neurodevelopmental disorders in childhood, characterized by difficulties with attention, hyperactivity, concentration, and impulse control. The global prevalence of ADHD is approximately 5%, with a higher incidence in boys compared to girls. Pharmacological treatments for ADHD include central nervous system stimulants, antidepressants, antipsychotics, anticonvulsants, anxiolytics, lithium, guanfacine, and clonidine. The side effects associated with these medications can include sleep disturbances, headaches, nausea, eating issues, aggression, malaise, growth retardation, mood swings, tics, and potential cardiac risks. This profile of side effects has prompted investigations into alternative treatment options for ADHD (36).

Fifty-four children, aged 6 to 17, who were diagnosed with ADHD according to the DSM-5, participated in a 6-week randomized, double-blind study designed to compare the effectiveness of saffron with methylphenidate in alleviating ADHD symptoms. Children in the saffron group received saffron capsules at a dosage of 20-30 mg per day, while the other children were administered methylphenidate at the same dosage of 20-30 mg per day. Changes in ADHD symptoms were evaluated using the Teacher and Parent Attention Deficit/Hyperactivity Disorder Rating Scale-IV at baseline and again at weeks 3 and 6. Findings from all evaluation scales indicated that there was no significant difference between the two groups ($F = 0.749$, $df = 1.317$, $p = 0.425$; $F = 0.249$, $df = 1.410$, $p = 0.701$, respectively), and also the frequencies of side effects were comparable (37).

Khaksarian et al. evaluated the efficacy of a combination of methylphenidate and saffron in 70 children (ages 6-16) diagnosed with ADHD. After dividing the patients into two equal groups, both groups received either 20 or 30 mg/day of methylphenidate (20 mg/day for those weighing less than 30 kg and 30 mg/day for those weighing more than 30 kg). Additionally, one of the groups was administered 20 or 30 mg/day of saffron capsules based on body mass index (20 mg/day for those under 30 kg and 30 mg/day for those over 30 kg). According to the Attention Deficit/Hyperactivity Disorder Rating Scale-IV, which was completed by both parents and teachers, both groups of patients exhibited fewer symptoms after eight weeks of treatment. After four weeks, the mean score of the methylphenidate-saffron combination group was lower than that of the methylphenidate group. In light of all the findings, it was concluded that using methylphenidate in combination with saffron would reduce the duration of treatment for ADHD patients while enhancing the treatment's effectiveness (38).

A single-center, prospective, naturalistic, non-randomized, non-blinded, pre-post intervention study was conducted on 63 children diagnosed with

ADHD according to DSM-5 criteria to evaluate the efficacy of saffron extract (Saffr'Activ) versus methylphenidate. Children were divided into two groups, with both groups receiving psychoeducation. Additionally, patients in Group 1 were administered slow-release methylphenidate at a dose of 1 mg/kg/day, while patients in Group 2 received saffron extract at a dosage of 30 mg/day. As a result of evaluations conducted using lens and pen-and-paper tests, it was observed that the effectiveness of saffron extract was comparable to that of methylphenidate. However, it was concluded that saffron was more effective for hyperactivity, while methylphenidate demonstrated greater effectiveness for concentration (39).

Pazoki et al. assessed the effectiveness of saffron extract as an adjunctive treatment in a placebo-controlled, double-blind, randomized clinical trial involving fifty-six patients diagnosed with ADHD over a period of six weeks. Patients were divided equally into two groups: one was given Ritalin plus placebo (30 mg/day), and the other Ritalin plus saffron (15 mg twice daily). The effectiveness of the treatments administered to the patients was assessed using the Conners Adult ADHD Rating Scale (CAARS) and the Adult ADHD Self-Report Scale (ASRS). It was found that there was no significant difference in the CAARS and ASRS scores, nor in the frequency of side effects, between the two groups at baseline and after treatment (40).

As a result of the search studies conducted using the keywords "attention deficit disorder with hyperactivity," "attention deficit," "ADHD," "hyperkinetic," or "minimal brain dysfunction" from the PubMed, EMBASE, Scopus, and Web of Knowledge databases, it was planned to evaluate the effectiveness of saffron in ADHD through a meta-analysis involving a total of four clinical studies. This analysis excluded non-English articles, review articles, comments, letters, observational studies, theses, animal studies, *in vitro* studies, and conference abstracts. The studies compared the effect of saffron with methylphenidate and displayed that the doses of saffron capsules generally ranged from 20 to 30 mg/day. Data from a total of 118 patients indicated that saffron capsules could be used alone or as an adjuvant to methylphenidate in ADHD with an acceptable safety profile (41).

5.3. Effects of *C. sativus* in Premenstrual Syndrome (PMS)

Premenstrual dysphoric disorder (PMDD) is a condition characterized by severe mood and behavioral changes. At present, the correlation between this disorder and alterations in serotonin conductance within the central nervous system has been validated by the positive effects observed with SSRI medications. In addition to the use of antidepressants for PMS, the utilization of herbal medicines with traditional medicinal origins is becoming increasingly common. For this purpose, it is essential to investigate the medicinal plants such as saffron, employed in traditional folk medicine for depressive disorders in clinical trials. Agha-Hosseini et al. conducted a double-blind, placebo-controlled study to investigate the efficacy of capsules containing dried *C. sativus* stigma extract on PMS symptoms. In the study, 78 women aged 20 to 45 who had regular menstrual cycles and experienced PMS symptoms for at least six months were assigned to receive either 15 mg saffron capsules twice daily (group A) or placebo capsules twice daily for two menstrual cycles (cycles 3 and 4). In the study evaluating efficacy using the Daily Symptom Report and the Hamilton Depression Rating Scale, findings indicated that saffron stigma extract was effective in alleviating PMS symptoms during the 3rd and 4th cycles (42).

Fukui et al.(43) designed a clinical study to explain the effects of saffron odor on PMS, dysmenorrhea, and irregular menstruation in 35 women with a normal sense of smell, measured salivary cortisol, testosterone, and 17-β estradiol levels, and used the State-Trait Anxiety Inventory. In the study, women were exposed to saffron odor for 20 minutes. At the end of this period, it was found that cortisol levels decreased significantly in both the follicular and luteal phases, while 17-β estradiol levels increased. Conversely, the State-Trait Anxiety Inventory scores decreased in both phases. The findings support the notion that the scent of saffron may have both physiological and psychological effects on PMS, dysmenorrhea, and irregular menstruation in women.

A randomized, triple-blind controlled clinical trial conducted in Iran on 78 students aged 18-35 investigated the efficacy of capsules containing 30 mg of dried saffron stigma extract in PMS. The study lasted for two menstrual cycles for both the intervention group and the group receiving the placebo capsules. The saffron capsules efficacy of based on the results from the DASS21 scale and the premenstrual symptom assessment forms. At the beginning of the study, there was no significant difference in the mean severity of PMS between the two groups. However, at the end of the study, the change in the mean severity of PMS was found to differ in the intervention group ($p<0.001$) compared to the placebo group ($p = 0.04$) from the beginning. The researchers concluded that saffron effectively reduces the severity of PMS symptoms; however, they noted that further clinical studies are necessary to reach a more definitive conclusion (44).

5.4. Effects of *C. sativus* for sleep quality

Sleep problems occur when a person does not get enough quality sleep. The problem can manifest in symptoms such as difficulty falling asleep, waking up frequently, waking up early, or not feeling refreshed after waking. Various factors, both physical and psychological, can lead to temporary or chronic sleep issues. Since saffron has traditionally been used to combat insomnia, this section of the review discusses several studies and their findings regarding its impact of saffron on sleep quality. It is know that people with diabetes experience deterioration in their sleep quality due to impaired glucose levels. In a placebo-controlled clinical study conducted in Iran in 2016 on 50 diabetic patients, the effects of oral saffron capsules on sleep quality were evaluated. The treatment group received 300 mg saffron capsules, while the control group received placebo capsules for a week. After treatment, the patient's sleep quality was evaluated with the Pittsburgh Sleep Quality Index, and a statistically significant difference was observed between the two groups. The study findings showed that saffron capsules may be effective in improving the sleep quality of diabetic patients (45).

In a meta-analysis conducted on improving sleep quality with saffron, articles published up to 2022 were accessed from PubMed, Central, Google Scholar, and Scopus databases. The Cochrane risk tool was used to prevent bias, and the methodological features of the articles were assessed using the Stevinson and Ernst criteria. As a result, five randomized clinical trials with 379 participants from three countries were found to meet the meta-analysis criteria. The duration of the studies ranged from four to eight weeks; four studies used saffron extract (14-28 mg/day), and one study used crocin (0.6 mg/day). The findings displayed that saffron positively affects the duration and the quality of sleep (46).

6. Toxicity and safety of *C. sativus*

LD_{50} values: 1.6 g/kg intraperitoneally for stigma in mice, >5000 mg/kg orally.

Human safe dose: <1.5 g/day is non-toxic. >5 g is toxic, >20 g is potentially fatal.

Clinical Doses: Generally in the range of 30–50 mg/day; found to be safe.

Common side effects: Dry mouth, dizziness, nausea, diarrhea. Generally mild and transient.

Serious effects (High doses): Numbness, jaundice, spontaneous bleeding, abnormal uterine bleeding (estrogenic effect).

Effects on organ systems: Liver/Kidney: Increased BUN and creatine at high doses; ineffective at low doses.

Coagulation: Decreased platelet count, altered clotting time (adenosine-induced).

Hormones/Lipids: No significant changes were detected.

Drug interactions are not yet known (47).

7. Conclusion

*C. sativus (*saffron), due to its rich profile of bioactive components, has transcended traditional applications and become a promising candidate for modern phytotherapeutic strategies. Recent studies have elucidated the mechanisms of action of its key constituents-crocin, crocetin, safranal, and picrocrocin-in various neuropsychiatric conditions.

Preclinical and clinical evidence supports saffron's effectiveness in managing neurological and psychiatric disorders. The proposed mechanisms of action in these disorders are as follows:

Mechanism of memory-enhancing and neuroprotective effects (in cognitive disorders): Saffron prevents β-amyloid plaque and tau protein accumulation, inhibits acetylcholinesterase activity, reduces neuronal apoptosis, and ameliorates neuroinflammation.

Mechanism of antidepressant effects: Saffron may inhibit the reuptake of dopamine and noradrenaline, enhance levels of brain-derived neurotrophic factor (BDNF), VGF neuropeptide, and cyclic AMP response element-binding protein (CREB), downregulate the hypothalamic-pituitary-adrenal (HPA) axis, and reduce neuroinflammation.

Mechanism of anxiolytic effects: It promotes neuronal growth and survival and may reduce neuronal excitability, contributing to decreased anxiety symptoms.

Mechanism of action in improving sleep disturbances: Saffron exerts sedative and calming effects, regulates the circadian rhythm by enhancing nocturnal melatonin secretion, and supports healthy sleep architecture.

Mechanism of action in ADHD: It modulates monoaminergic and glutamatergic neurotransmission, thereby reducing hyperactivity and impulsivity.

Mechanism of action in obsessive-compulsive disorder (OCD): Saffron increases serotonergic activity, elevates brain zinc levels, and may potentiate antipsychotic-like effects.

All of these findings suggest that *C. sativus* may be considered as a complementary option in the treatment of depression and ADHD; however, larger-scale and long-term studies are needed. The biggest shortcoming of clinical studies to date is that few studies have used standardized extract formulations, and there is some methodological heterogeneity. Therefore, large-scale, randomized, placebo-controlled studies are needed to confirm that saffron safety, effectiveness, and its role in pharmacologically predictable treatment for neuropsychiatric disorders such as depression and ADHD. Furthermore, detailed studies on its pharmacokinetics, dose-response relationships, and long-term safety profiles are vital. Future research in these areas will not only strengthen the scientific basis for the use of saffron in modern psychopharmacology but may also accelerate the development of new, plant-based therapeutic interventions.

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Ethics approval: Not applicable

References

1. Uslu E, Babaç MT, Bakış Y. Investigations on anatomical and morphological characteristics of some Crocus L. taxa around Abant Lake. Ant J Bot. 2022;6(2):122-131. https://doi.org/10.30616/ajb.1174440
2. Mathew BF. Flora of Turkey and the East Aegean Islands. Edinburgh: Edinburgh University Press; 1984. Crocus; 8:413-438.
3. Özhatay N.Diversity of bulbous monocots in Turkey with special reference.Chromosome numbers.Pure Appl Chem.2002;74(4):547-555. https://doi.org/10.1351/pac200.274.040547
4. Alavi-Kia S, Mohammadi S, Aharizad S, Moghaddam M. Analysis of genetic diversity and phylogenetic relationships in Crocus genus of Iran using inter retrotransposon amplified polymorphism. Biotechnol Biotechnol Equip. 2008;22(3):795-800. https://doi.org/10.1080/13102.818.2008.10817555
5. Kerndorff H, Pasche E, Harpke D, Blattner F. Seven new species of Crocus (Liliiflorae, Iridaceae) from Turkey. Stapfia. 2012;97:3-16.
6. Yüzbaşıoğlu S, Aslan S, Özhatay N. Crocus thracicus (Iridaceae), a new species from north-western Turkey. Phytotaxa. 2015;197(3):207-14. https://doi.org/10.11646/phytotaxa.197.3.4
7. Erol O, Çiftçi A. Resimli Türkiye Florası.İstanbul: Ali Nihat Gökyiğit Vakfı Yayınları; 2022. Crocus; p.482-95.
8. Gümüş YA. Folkloric investigation of saffron plant and saffron culture in Safranbolu district. IJAH. 2021;2(1):1-23.
9. Saffron Production Trade and Consumption A 360° Industry Report [Internet]. By Ess Team; 2025 [cited 2025 Mar 17]. Available from: https://essfeed.com/saffron-production-trade-and-consumption-a-360-industry-report-saffron-production-trade-and-consumption-a-360-industry-report/
10. Mohtashami L, Amiri MS, Ramezani M, Emami SA, Simal-Gandara J. The genus Crocus L.: A review of ethnobotanical uses, phytochemistry and pharmacology. Ind Crops Prod. 2021;171:113923. https://doi.org/10.1016/j.indcrop.2021.113923
11. Paşayeva L, Tekiner H. Türk İslam Tıbbında Safranın Yeri. MUTFTD. 2014;4(3):11-5.
12. Gürbüz A. Şifalı Nebatlar. İstanbul: Bayram Yayımcılık; 1982.
13. Saxena RB. Botany, Taxonomy and Cytology of Crocus sativus series. AYU. 2010;31(3):374-81. https://doi.org/10.4103/0974-8520.77153

14. Crocus sativus L. Plants of the World Online (POWO) [Internet]; 2025 [cited 2025 Mar 7]. Available from: https://powo.science.kew.org/taxon/urn:lsid:ipni.org:names:436688-1
15. Crocus sativus L./Safran [Internet]. Türkiye; 2025 [cited 2025 Mar 7]. Available from: https://turkiyeflorasi.org.tr/taxon/6e44bed3-22f9-40e0-86c5-2ca44034775a
16. 16. Srivastava R, Ahmed H, Dixit RK, Dharamveer SAS. Crocus sativus L.: A comprehensive review. Pharmacog Rev. 2010;4(8):200-8. https://doi.org/10.4103/0973-7847.70919
17. Matraszek-Gawron R, Chwil M, Terlecki K, Skoczylas MM. Current Knowledge of the Antidepressant activity of chemical compounds from Crocus sativus L. Pharmaceuticals. 2023;16:58. https://doi.org/10.3390/ph16010058
18. Anaeigoudari F, Anaeigoudari A, Kheirkhah-Vakilabad A. A review of therapeutic impacts of saffron (Crocus sativus L.) and its constituents. Physiol Rep. 2023;11:e15785. https://doi.org/10.14814/phy2.15785
19. Bukhari SI, Manzoor M, Dhar MK. A comprehensive review of the pharmacological potential of Crocus sativus and its bioactive apocarotenoids. Biomed Pharmacother. 2018;98:733-45. https://doi.org/10.1016/j.biopha.2017.12.090
20. Akhondzadeh S, Fallah-Pour H, Afkham K, Jamshidi AH, Khalighi-Cigaroudi F. Comparison of Crocus sativus L. and imipramine in the treatment of mild to moderate depression: A pilot double-blind randomized trial. BMC Complement Altern Med. 2004;4:12. https://doi.org/10.1186/1472-6882-4-12
21. Akhondzadeh S, Tahmacebi-Pour N, Noorbala AA, Amini H, Fallah-Pour H, Jamshidi AH, Khani M. Crocus sativus L. in the treatment of mild to moderate depression: a double-blind, randomized and placebo-controlled trial. Phytother Res. 2005;19:148-51. https://doi.org/10.1002/ptr.1647
22. Noorbala AA, Akhondzadeh S, Tahmacebi-Pour N, Jamshidi AH. Hydro-alcoholic extract of Crocus sativus L. versus fluoxetine in the treatment of mild to moderate depression: a double-blind, randomized pilot trial. J Ethnopharmacol. 2005;97:281-284. https://doi.org/10.1016/j.jep.2004.11.004
23. Akhondzadeh Basti A, Moshiri E, Noorbala AA, Jamshidi AH, Abbasi SH, Akhondzadeh S. Comparison of petal of Crocus sativus L. and fluoxetine in the treatment of depressed outpatients: A pilot double-blind randomized trial. Prog Neuropsychopharmacol Biol Psychiatry. 2007;31:439-442. https://doi.org/10.1016/j.pnpbp.2006.11.010
24. Hausenblas HA, Saha D, Dubyak PJ, Anton SD. Saffron (Crocus sativus L.) and major depressive disorder: a meta-analysis of randomized clinical trials. J Integr Med. 2013;11(6):377-383. https://doi.org/10.3736/jintegrmed2013056
25. Shahmansouri N, Farokhnia M, Abbasi SH, Kassaian SE, Noorbala Tafti AA, Gougol A, Yekehtaz H, Forghani A, Mahmoodian M, Saroukhani S, Arjmandi-Beglar A, Akhondzadeh S. A randomized, double-blind, clinical trial comparing the efficacy and safety of Crocus sativus L. with fluoxetine for improving mild to moderate depression in post percutaneous coronary intervention patients. J Affect Disord. 2014;155:216-222. https://doi.org/10.1016/j.jad.2013.11.003
26. Maryam AT, Moghadam H, Tabassi SAS, Mohajeri SA. Crocin, the main active saffron constituent, as an adjunctive treatment in major depressive disorder: A randomized, double-blind, placebo-controlled, pilot clinical trial. J Affect Disord. 2015;174:51-56. https://doi.org/10.1016/j.jad.2014.11.035
27. Sahraian A, Jelodar S, Javid Z, Mowla A, Ahmadzadeh L. Study the effects of saffron on depression and lipid profiles: A double blind comparative study. Asian J Psychiatr. 2016;22:174-176. https://doi.org/10.1016/j.ajp.2015.10.012
28. Mazidi M, Shemshian M, Mousavi SH, Norouzy A, Kermani T, Moghiman T, Sadeghi A, Mokhber N, Ghayour-Mobarhan M, Ferns GAA. A double-blind, randomized and placebo controlled trial of Saffron (Crocus sativus L.) in the treatment of anxiety and depression. J Complement Integr Med. 2016;13(2):195-199. https://doi.org/10.1515/jcim-2015-0043
29. Shahdadi H, Balouchi A, Dehghanmehr S. Effect of saffron oral capsule on anxiety and quality of sleep of diabetic patients in a tertiary healthcare facility in southeastern Iran: A quasi-experimental study. Trop J Pharm Res. 2017;16(11):2749-2753. https://doi.org/10.4314/tjpr.v16i11.24
30. Jafarnia N, Ghorbani Z, Nokhostin M, Manayi A, Nourimajd S, Jahromi SR. Effect of Saffron (Crocus sativus L.) as an add-on therapy to sertraline in mild to moderate generalized anxiety disorder: A double blind randomized controlled trial. Arch Neurosci. 2017;4(4):e14332. https://doi.org/10.5812/archneurosci.14332
31. Lopresti AL, Drummond PD, Inarejos-García AM, Prodanov M. affron®, a standardised extract from saffron (Crocus sativus L.) for the treatment of youth anxiety and depressive symptoms: A randomised, double-blind, placebo-controlled study. J Affect Disord. 2018;232:349-357. https://doi.org/10.1016/j.jad.2018.02.070
32. Tóth B, Hegyi P, Lantos T, Szakács Z, Kerémi B, Varga G, Tenk J, Pétervári E, Balaskó M, Rumbus Z, Rakonczay Z, Bálint ER, Kiss T, Csupor D. The Efficacy of Saffron in the Treatment of Mild to Moderate Depression: A Meta-analysis. Planta Med. 2019;85(1):24-31. https://doi.org/10.1055/a-0660-9565
33. Marx W, Lane M, Rocks T, Ruusunen A, Loughman A, Lopresti A, Marshall S, Berk M, Jacka F, Dean OM. Effect of saffron supplementation on symptoms of depression and anxiety: a systematic review and meta-analysis. Nutr Rev. 2019;77(8):557-571. https://doi.org/10.1093/nutrit/nuz023
34. Khaksarian M, Behzadifar M, Behzadifar M, Alipour M, Jahanpanah F, Simona T, Firenzuoli F, Zerbetto R, Bragazzi NL. The efficacy of Crocus sativus (Saffron) versus placebo and Fluoxetine in treating depression: a systematic review and meta-analysis. Psychol Res Behav Manag. 2019;12:297-305. https://doi.org/10.2147/PRBM.S199343
35. Han S, Cao Y, Wu X, Xu J, Nie Z, Qiu Y. New horizons for the study of saffron (Crocus sativus L.) and its active ingredients in the management of neurological and psychiatric disorders: A systematic review of clinical evidence and mechanisms. Phytother Res. 2024;38:2276-2302. https://doi.org/10.1002/ptr.8110
36. Özbay A, Kayhan Z. Dikkat eksikliği ve hiperaktivite bozukluğunun (DEHB) nedenleri ve tedavi yöntemleri. ESOSDER. 2024;23(89):394-406. https://doi.org/10.17755/esosder.1283141
37. Baziar S, Aqamolaei A, Khadem E, Mortazavi SH, Naderi S, Sahebolzamani E, Mortezaei A, Jalilevand S, Mohammadi MR, Shahmirzadi M, Akhondzadeh S. Crocus sativus L. versus methylphenidate in treatment of children with attention-deficit/hyperactivity disorder: A randomized, double-blind pilot study. J Child Adolesc Psychopharmacol. 2019;29(3):205-212. https://doi.org/10.1089/cap.2018.0146
38. Khaksarian M, Mirr I, Kordian S, Nooripour R, Ahangari N, Masjedi-Arani A. A Comparison of methylphenidate (MPH) and combined methylphenidate with Crocus sativus (saffron) in the treatment of children and adolescents with ADHD: a randomized, double-blind, parallel-group clinical trial.

Iran J Psychiatry Behav Sci. 2021;15(3):e108390. https://doi.org/10.5812/ijpbs.108390

39. Blasco-Fontecilla H, Moyano-Ramírez E, Méndez-González O, Rodrigo-Yanguas M, Martin-Moratinos M, Bella-Fernández M. Effectivity of saffron extract (Saffr'Activ) on treatment for children and adolescents with attention deficit/hyperactivity disorder (ADHD): A clinical effectivity study. Nutrients. 2022;14:4046. https://doi.org/10.3390/nu14194046
40. Pazoki B, Zandi N, Assaf Z, Moghaddam HS, Zeinoddini A, Mohammadi MR, Akhondzadeh S. Efficacy and safety of saffron as adjunctive therapy in adults with attention-deficit/hyperactivity disorder: A randomized, double-blind, placebo-controlled clinical trial. AIMED. 2022;9(1):37-43. https://doi.org/10.1016/j.aimed.2022.01.002
41. Seyedi-Sahebari S, Farhang S, Araj-Khodaei M, Akhondzadeh S, Naseri A, Sanaie S, Frounchi N. The Effects of Crocus sativus (Saffron) on ADHD: A systematic review. J Atten Disord. 2024;28(1):14-24. https://doi.org/10.1177/108.705.47231203176
42. Agha-Hosseini M, Kashani L, Aleyaseen A, Ghoreishi A, Rahmanpour H, Zarrinara AR, Akhondzadeh S.Crocus sativus L.(saffron) in the treatment of premenstrual syndrome: a double-blind, randomised and placebo-controlled trial. BJOG. 2008;115:515-19. https://doi.org/10.1111/j.1471-0528.2007.01652.x
43. Fukui H, Toyoshima K, Komaki R. Psychological and neuroendocrinological effects of odor of saffron (Crocus sativus). Phytomedicine. 2011;18:726-30. https://doi.org/10.1016/j.phymed.2010.11.013
44. Beiranvand SP, Beiranvand NS, Moghadam ZB, Birjandi M, Azhari S, Rezaei E, Salehnia AN, Beiranvand S. The effect of Crocus sativus (saffron) on the severity of premenstrual syndrome. Eur J Integr Med. 2016;8:55-61. https://doi.org/10.1016/j.eujim.2015.06.003
45. Dehghanmehr S, Shadadi H, Mansouri A, Arbabisarjou A. Effect of oral saffron capsules on sleep quality in patients with diabetes at Zabol-Iran. Bali Med J. 2017;6(3):595-600. https://doi.org/10.15562/bmj.v6i3.623
46. Rafiei SKS, Abolghasemi S, Frashidi M, Ebrahimi S, Gharei F, Razmkhah Z, Tavousi N, Mahmoudvand B, Faani M, Karimi N, Abdi A, Soleimanzadeh M, Ahmadpour Youshanlui M, Sadatmadani SF, Alikhani R, Pishkari Y, Deravi N. Saffron and sleep quality: A systematic review of randomized controlled trials. Nutr Metab Insights. 2023;16:1-7. https://doi.org/10.1177/117.863.88231160317
47. Moshiri M, Vahabzadeh M, Hosseinzadeh H.Clinical applications of Saffron (Crocus sativus) and its constituents: A Review. Drug Res. 2015;65:287-295. https://doi.org/10.1055/s-0034.137.5681

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