

# Saffron for mood improvement in children and adolescents: a narrative review

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## Abstract

Depressive and anxious disorders could be experienced by children and adolescents worldwide and are associated with psychiatric syndromes diagnosed in adulthood. In this context, the COVID-19 outbreak and digital media arising use have worsened mental conditions in the pediatric population. Older adolescents, girls, and patients living with neurodiversity and/or chronic physical conditions are more likely to develop negative mental health outcomes.

*Crocus sativus L.* (saffron) is a medicinal plant whose most biologically relevant components are two carotenoids (crocin and crocetin) and two apocarotenoids (picrocrocin and safranal). Crocin seems to inhibit the uptake of dopamine and norepinephrine, while safranal inhibits the serotonin reuptake; *in vitro* and in animal models, crocin also displayed neuroprotective abilities, increasing the intracellular levels of neurotrophic factors. Further studies are required to strengthen these results; however, multiple studies have already demonstrated significant positive effects of saffron on psychiatric disorders – including depression and anxiety in young patients. Saffron administration appears to reduce depression symptoms and to strengthen antidepressant effects of current drugs (fluoxetine), also lowering adverse events of these therapies. Consequently, saffron could have an important role as a complementary therapy for depressive and anxious disorders in children and teenagers.

## Keywords

Saffron, children and adolescents, mood disorders, depression, anxious disorders.

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## Introduction

In the last decades, depression has been estimated to affect 2-8% of children and adolescents worldwide, with a peak incidence around puberty. It may be self-limiting, but about 40% of the above experience a recurrent attack, a third of affected children will make a suicide attempt, and 3-4% will die from suicide [1]. Adolescent-onset depression had worse outcomes than child-onset one; anyway, symptoms of depression that appear in adolescence and throughout childhood are associated with more frequent psychiatric disorders in adulthood [2]. Just before the COVID-19 outbreak in Italy, access to Child and Adolescent Neuropsychiatry Services concerned 6% of resident minors, against an estimated demand – also in accordance with international data – more than doubled [3]. The pandemic clearly worsened mental conditions in the pediatric population: a distinctive amount of depressive and anxious symptoms are now present, compared with prepandemic estimates. Recent evidence shows that children and adolescents who underwent lockdown and quarantine are 5 times more likely to require a mental health service input [4], whereas the pandemic effect was a decrease in depression screening at primary care visits. The percentage of adolescents who have been shown to present depressive symptoms is increased from 5% to more than 6%; positive suicide risk screens are increased from 6% to 7%, especially among female adolescents [5]. Older adolescents, girls, and patients living with neurodiversity and/or chronic physical conditions were more likely to experience negative mental health outcomes [6].

Adolescence is a period of often difficult transition and maturation towards adulthood, in which a high level of vulnerability is experienced. In this context, the COVID-19 pandemic has posed an unprecedented threat to global mental health of children and adolescents, due to both home confinement and physical distancing mandates – with larger abuse of digital media communication – and fear of the virus itself. Indeed, recent studies show that the COVID-19 pandemic acts as an important trigger to pediatric psychiatric disorders, such as post-traumatic stress disease, anxiety, and

depression. Lockdown isolation, in particular, had multiple negative effects on the health of the pediatric population: it is associated with school disruption, sudden separation from the peers, ubiquitous issue of death and worry for relatives and families, but also with a disruption of sleep patterns and decreased physical activity [7]. Moreover, family confinement could act as a potential trigger for intrafamilial violence [8].

Another body of research underlines the growing relationship established between digital media and depression: anxiety and depression could be associated with technology-based negative social comparison; anxiety results from a lack of emotion-regulation skills because of substituted digital media use; social anxiety derives from avoidance of social interaction because of substituted digital media use; anxiety arises because of worries about being inadequately connected; anxiety, depression, and suicide could be the result of cyberbullying and related behavior [9].

## General pharmacokinetics properties of saffron

*Crocus sativus L.* (saffron) is a medicinal plant, cultivated in different countries around the globe and variously used in cooking, food coloring, perfumes, and cosmetics [10]. Saffron's beneficial properties on health have been known for centuries and widely used by traditional medicine practice [11]. Only in the last decade, saffron was extensively studied from a scientific point of view, due to its interesting medical properties, leading to a more diffuse use of this medicinal plant in modern medicine [12].

Among more than 100 chemical compounds identified in saffron, the most biologically relevant components resulted to be two carotenoids (crocin and crocetin) and two apocarotenoids (picrocrocin and safranal). The amount of saffron active compounds varies from country to country and can be influenced by the quality of this medicament plant. In particular quality of saffron can be influenced by post-harvesting conditions like temperature, pH, light and oxygenation. For example, a prolonged drying of saffron at low temperatures can cause biodegradation of crocins, while a conservation at temperatures above 30°C usually enables to retain the biologically active compounds [10].

In the human body, the gastrointestinal tract is the main site of absorption of saffron, when administered orally. A preliminary hydrolysis is required for crocin to be absorbed by passive diffusion into the enterocytes as crocetin, which

results to be more hydrophilic. This compound is subsequently transported via the lymphatic system into the bloodstream. Studies have reported the ability of crocetin to pass the brain barrier, therefore reaching the central nervous system (CNS). Moreover, in the CNS, crocetin has shown a high affinity for neural N-methyl-D-aspartate receptors (NMDAr) [13]. This compound is rapidly metabolized in glucuronide conjugates and thus easily distributed in various tissues of the body, including nervous tissue. Unlike for other carotenoids, the rapid metabolism of crocetin does not allow its accumulation in plasma [10, 11].

### General pharmacological activity of saffron

Saffron resulted to have many important biological properties. Some saffron compounds have strong antioxidant and anti-inflammatory properties, thus potentially managing to prevent cancer, aging and other diseases. In particular, safranal and crocin can successfully capture free radicals, while crocetin can remove them and inhibits lipids' peroxidation. Moreover, crocin has the ability to inhibit cyclooxygenase-1 (COX1) and cyclooxygenase-2 (COX2) and to block prostaglandin E2 (PGE2) production. These important properties of saffron also inhibit overproduction of cytokines during inflammatory states [14-17]. Many studies also demonstrated that saffron has an important role in the regulation of the cardiovascular system [18, 19] and hyperglycemia lowering effects [20], thanks to its antioxidant properties.

Nevertheless, the most notable identified biological properties of this herbal plant are on the CNS. Crocin is able to inhibit the uptake of dopamine and norepinephrine, while safranal seems to inhibit the serotonin reuptake. Moreover, *in vitro* and in animal models, crocin also displayed neuroprotective abilities, increasing the intracellular levels of neurotrophic factors, such as brain-derived neurotrophic factor (BDNF). However, further studies are anyway required to strengthen these hypotheses [21-23]. Multiple studies have demonstrated significant positive effects of saffron on psychiatric disorders – including depression, anxiety, and memory-related degenerative disturbs [23]. Concerning depression, evidence in the literature showed that, in adult patients affected with mild to moderate depression, saffron has a positive effect on the symptoms of this disease and that could strengthen the effect of the commonly used antidepressants.

For what concerns schizophrenia, studies on animal models showed a positive effect of saffron in reversing negative side effects of ketamine and other evidence in human patients later confirmed the high tolerability of this compound in this kind of patients. Saffron was beneficial in reducing symptoms and comorbidity rates in the treatment of anxiety and bipolar disorders. Moreover, due to its neuroprotective effects, saffron can also be used in the management of patients with mild to moderate Alzheimer's disease: evidence shows that the use of this compound alongside standard therapy allows patients to reach a substantial clinical stability of the cognitive impairment (assessed with appropriate scores) [23].

### Saffron and depressive and anxiety disorders therapy in adolescence

Depression is a diffuse mental disorder in adolescents, characterized by a high load of disease and whose main treatment consists in various classes of antidepressant molecules. Antidepressants have a great impact on depression symptoms, but they are burdened with low tolerability and low chances of inducing proper remission. Concerning anxiety, alongside the burden of disease also lies an insufficient short- and long-term efficacy of the current therapies, which also are responsible for adverse effects when administered for a long period [23, 24]. Alongside standard therapies, psychotherapy and cognitive-behavioral interventions can be possible complementary interventions in order to support not only the patients but also their family.

Indeed, there has been a growing interest in psychoeducational interventions (PIs) [25]. A meta-analysis of Donker et al. revealed that brief passive good-quality PIs can reduce symptoms of depression and psychological distress. It has been demonstrated that also a single-session intervention can have a positive effect in reducing symptoms of psychological discomfort, even in the highly stressful COVID-19 pandemic context of life [26].

PIs can be subsequently considered as a first-step intervention for patients experiencing psychological distress or depression and might serve as an initial intervention in primary care or community models [26]. Different programs and approaches are available and can be directed not only towards the single patient, but also to patients' families or school groups. Moreover, PIs can benefit from different forms of communication (telemedicine, online and

phone tools), thus increasing compliance. Indeed, as demonstrated in the literature, programs and methods of communication are adapted in order to gain maximum interaction with patients of younger age, such as teenagers. A systematic review by Bevan Jones et al. describes the evidence of the effectiveness of PIs for adolescents with or at high risk of depression [27]. Though, for the moment, evidence is limited, a range of potential benefits has been reported, such as modification of behavior and attitudes in adolescents and improvement of family communication to achieve a positive effect on mood symptoms and wellbeing. Though PIs can have a role in preventing/managing adolescent depression, as a first-line or adjunctive approach, the limited number of studies, heterogeneity in formats and evaluation, and inconsistent approach to defining PI, make it difficult to compare programs and measure overall effectiveness [27].

Unfortunately, in younger patients, a great obstacle is the low tolerance and compliance towards the proposed therapies (both pharmacological and non-pharmacological, such as PIs and psychotherapy). Considering all these aspects, a less toxic therapy for both depressive and anxiety disorders is needed, also considering increased new diagnoses due to the COVID-19 pandemic.

Due to its neuroprotective properties, saffron has been recently studied as a good complementary treatment to antidepressants in patients diagnosed with mild to moderate depression [24]. In fact, many studies showed that saffron has a great ability to reduce depression symptoms [28-32], above all if compared to placebo [24]. In particular, it appeared to have a great effect on social phobia, separation anxiety and overall depression.

Saffron is also shown to strengthen antidepressant effects of current drugs, such as fluoxetine, also lowering adverse events of these therapies [23, 29]. Moreover, no side effects caused by saffron, in addition to the ones already due to antidepressants or other anti-anxiety medications, were described in the literature [24, 32]. These findings were reported not only in adults but also in adolescents, in which saffron was even suggested as depression treatment due to the higher tolerability, compared to the normally used drugs [33, 34].

## Conclusion

Children and adolescents can be widely affected by anxious and depressive disorders; digital media spreading and the COVID-19 pan-

demical outbreak doubled for many reasons the incidence of these disorders. A limited number of studies result to be available concerning the use of saffron in the treatment of mood disorders in adolescents; nonetheless, currently available results are interesting: saffron administration appears to reduce depression symptoms and to strengthen antidepressant effects of current drugs (fluoxetine), also lowering adverse events of these therapies. Consequently, saffron could have an important role as a complementary therapy for depressive and anxious disorders in children and teenagers.

## Declaration of interest

The Authors declare that there is no conflict of interest.

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