Saffron: Health Benefits of Crocus sativus L.

THE WORLD’S MOST VALUABLE HERB

By Dr. Traj Nibber, Founder and CEO of Advanced Orthomolecular Research

BACKGROUND:
SAFFRON: CULTIVATING “RED GOLD”

Saffron (Crocus sativus L.) is a vibrantly orange herb, grown only in very specific regions of the world including Afghanistan, Greece, Turkey, Iran and Spain, with Iran accounting for over 90% of global production. Saffron is harvested in mid-October, with the fragile stigmas picked by hand. It takes over 200,000 dried stigmas, obtained from about 70,000 flowers, to yield around 500 g of pure saffron. The whole process is laborious and very costly, and as a result, saffron has been described as the most expensive herb in the world. In Iran, it is referred to as “Red Gold.” Because of the cost, saffron is highly prone to being adulterated with other herbs and therefore, it can be challenging to obtain pure saffron (Petrakis et al., 2015).

For millennia, saffron has been used as a food colourant and preservative, as well for medicinal and religious purposes. It is a staple in Middle Eastern, Chinese and Indian cuisine.

THE COMPOSITION OF SAFFRON

Saffron contains over 150 different components, at least 50 of which have been identified. They include three major categories: carotenoids, terpenes and flavonoids (Srivastava et al., 2010).

The red stigmatic lobes of the Crocus sativus flower contain three main active compounds:

1. **Crocins**, which are saffron-colored compounds (unusual water-soluble carotenoids due to their high glycosyl contents)
2. **Picrocrocins**, which are the main substances responsible for saffron’s bitter taste
3. **Safranal**, which is the volatile oil responsible for the characteristic saffron aroma

The chemical structures of the saffron bio-actives are illustrated in Figure 2.

The carotenoids are sensitive to light, heat and oxygen so special precautions must be taken during every step of processing from raw material to finished product.

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**Figure 1. Saffron petal and the prized stigmas.**

**Figure 2. Chemical structures of saffron bio-actives.**
(Source: Rezaee Khorasany & Hosseinzadeh, 2016, p. 458)
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THERAPEUTIC BENEFITS OF SAFFRON

A large body of clinical research has been published on saffron, with Iranians leading the world in this research. We can categorize it into four major areas:

1. Central nervous system (CNS) actions: antidepressant/antianxiety, cognitive and neuroprotective effects, and ADHD
2. Diabetes and metabolic syndrome
3. Cardiovascular and heart disease
4. Sexual health

CNS ACTIONS

Antidepressant and Antianxiety Effects

The strongest evidence exists to support the efficacy of saffron for improving symptoms of mild to major depressive disorder (MDD). Saffron has been studied for mood and anxiety in over 20 human studies, including clinical studies of saffron and depression and anxiety, as listed in the Appendix of this White Paper.

The mechanism of action of saffron is thought to be similar to that of prescription antidepressants: re-uptake inhibition of monoamines (dopamine, norepinephrine and serotonin), inhibiting the N-methyl-D-aspartic acid (NMDA) receptor. It also has GABA-like effects. A recent study suggests that the capacity of saffron to reduce homocysteine levels may also be a contributing factor to its effectiveness (Jelodar et al., 2018).

In clinical studies, saffron not only had significantly greater antidepressant properties compared to placebo, but it was also shown to be as effective as conventional antidepressants such as imipramine and fluoxetine (Prozac) (Akhondzadeh Basti et al., 2007).

Figure 3. Possible mechanisms of action of saffron in depression.
(Source: Skaper et al., 2018, p. 15)

Figure 4. Saffron vs. imipramine head-to-head comparison for treatment of depression.
(Akhondzadeh et al., 2004)

Figure 5. Saffron vs. fluoxetine head-to-head comparison for the treatment of depression.
(Noorbala et al., 2005)

Haunenblas et al. (2013) conducted a meta-analysis of five published randomized controlled trials examining the effects of saffron supplementation on symptoms of depression among participants with MDD. They found a large effect size for saffron supplementation compared to placebo in treating depressive symptoms ($P <0.001$) and found a null effect size between saffron supplementation and antidepressant groups ($MES = -0.15$; study $n=3$). These results indicate that saffron supplementation significantly reduced...
depression symptoms compared to placebo, and there was little or no difference between the efficacy of saffron and antidepressants.

A study by Shahmansouri et al. (2014) examined the effects of saffron supplementation versus fluoxetine in heart patients with MDD who had undergone percutaneous coronary intervention. The researchers found that short-term therapy (six weeks) with saffron supplementation produced similar improvements in symptoms of depression as the antidepressant medication.

A later meta-analysis, by Lopresti and Drummond (2017), confirmed the results of the earlier meta-analysis: that in the placebo-comparison trials, saffron had large treatment effects, and when compared with antidepressant medications, had similar antidepressant efficacy. There was no statistical difference in adverse effects between placebo or saffron, highlighting the safety of saffron treatment. Most recently, a meta-analysis by Tóth et al. (2019) found saffron to be effective in MDD.

In a recent double-blind randomized clinical study by Ghajar et al. (2017), saffron was compared to citalopram, the latest benzodiazepine prescription drug, in the treatment of mild to moderate depression with accompanying anxiety (30 patients in each group). Saffron was demonstrated to be as safe and effective as citalopram in the six weeks trial. Clinical relevance was emphasized by the improvements in scores for both groups in the two standard clinical measures: Hamilton Depression (HAM-D) and Hamilton Anxiety (HAM-A). Moreover, similar doses – 30 mg saffron versus 40 mg citalopram – were used in the study, which is important because often the dose of the herb is five to ten-fold higher than the prescription drug. The researchers speculated that higher doses of saffron might exert even greater beneficial effects.

In a study of mothers with mild to moderate postpartum depression, the researchers reported the positive effects of saffron in reducing the anxiety and improving mood (Tabeshpour et al., 2017).

**COGNITIVE EFFECTS**

**Parkinson’s and Alzheimer’s Diseases**

Animal studies using saffron have shown neuroprotective effects in a model of Parkinson’s disease, preventing memory impairment and enhancing spatial cognitive abilities after chronic cerebral hypoperfusion. Several human studies have been conducted in patients with Parkinson’s disease, and while the number of patients was small, the results nonetheless confirmed the animal studies.

Alzheimer’s disease is the most common form of dementia, in which the death of brain cells causes memory loss and cognitive decline. Several factors are thought to play roles in the development and course of Alzheimer’s disease. Existing medical therapies, unfortunately, only modestly alleviate and delay cognitive symptoms.

Current research has focused on developing therapies to remove the aggregates of amyloid-β (Aβ) and tau protein, which are thought to be causative factors. The biological properties of saffron, and particularly its main constituent crocin, have been studied extensively for many conditions including dementia and traumatic brain injury.

**Crocin**

Crocin is a unique antioxidant, because it is a water-soluble carotenoid. Finley and Gao (2017) discuss the multifunctional protective activities of crocin in the brain and point to its promising role as a supplement or as a drug for prevention or treatment of Alzheimer’s disease.

**Akhondzadeh’s Study**

One of the giants in saffron research, and colleagues conducted a 16-week, double-blind, placebo-controlled study of saffron in patients with mild to moderate Alzheimer’s disease. Cognitive function measures of the 46 patients in the study showed significantly better outcome for those who received 30 mg/day saffron compared to placebo (Akhondzadeh et al., 2010).

In a clinical study on cognition, an ethanolic extract of saffron was found to have the same activity as the prescription drugs donepezil and memantine in reducing the cognitive decline in patients with mild to moderate and moderate to severe Alzheimer’s disease (Farokhnia et al., 2014). Side-effects were no different to placebo. The study period was only a few months, which is a short time for treatment considering the nature of the disease. A longer duration and a higher dose study may perhaps yield even better results.

**Schizophrenia**

Thus far, only one clinical trial has been performed to assess the safety and tolerability (but not the efficacy) of saffron in schizophrenia. This double-blind placebo-controlled study was...
carried out in 61 schizophrenia patients, who received twice-daily treatment of saffron (standardized for crocin 15 mg) or placebo for 12 consecutive weeks. The results of this study confirmed the safety of saffron, and showed improvement in various parameters of the disease as well. The proposed mechanism of action suggests that the reduction of glutamate levels caused by saffron and its constituents might be the reason for the beneficial action exerted by the active crocins, although it may also be due to their powerful antioxidant properties (Mousavi et al., 2015).

Attention-Deficit/Hyperactivity Disorder
In a study of saffron's effect in attention-deficit hyperactivity disorder (ADHD), Baziar et al. (2019) compared saffron to Ritalin (methylphenidate) in a randomized, double-blind, placebo-controlled study with 54 children (ages 7-17 years) for six weeks. The doses used were similar, either 20 to 30 mg methylphenidate or 20 to 30 mg saffron extract. Symptoms were assessed using the Teacher and Parent Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) at baseline and at weeks three and six. The results were remarkably similar; that is, there was no difference between the effectiveness of the two formulations.

This is a hugely interesting finding considering ADHD is one of the most common mental disorders with prevalence of 3-7% among school-age children, and its symptoms persist in 60% of adults. It is estimated that the incidence of ADHD in adults is 4%. In addition, 30% of children with ADHD do not respond to methylphenidate, and its side-effects usually force patients to give up their therapy (Spencer et al., 1996). Although this study must be considered preliminary until more studies are conducted, it is nonetheless a significant advancement in ADHD research.

Diabetic and Metabolic Syndrome Effects
In a randomized, single-blind, placebo-controlled clinical trial in patients with type II diabetes mellitus (n=208), saffron was tested against cinnamon, cardamom and ginger. These various herbal supplements showed significant beneficial effects on cholesterol, but not glycemic control, oxidative stress and inflammation (Azimi et al., 2014). In a different study, however, saffron hydro-alcoholic extract was found to improve blood glucose control by decreasing fasting blood sugar in patients with type II diabetes mellitus (n=54) (Milajerdi et al., 2018). Recently, Jam et al. (2017) reported reduction of lipid levels in their study of the effect of crocin on depressive symptoms in patients with metabolic syndrome.

Cardiovascular Effects
Cardiovascular disease (CVD) covers numerous conditions, including myocardial infarction, heart failure and stroke. Inflammation plays an essential role in the atherosclerosis of CVDs. During the early stage of atherogenesis, inflammation in the innermost layer of the vessels induces a host of proinflammatory mediators, including cytokines and chemokines, as well as releasing adhesion molecules that cause “stickiness” of lipids, cells, debris and other minerals and forms a plaque.

In addition, oxidative stress may also play an important role in atherogenesis. This is a process wherein there is overproduction of reactive oxygen species (ROS), which may also be one of the initiating events in inflammation. Saffron has powerful antioxidant capacity, and along with its calcium channel blocking effect, may result in the relaxation of blood vessels that leads to a hypotensive effect and decrease in the mean arterial blood pressure.

Cholesteryl ester transfer protein (CETP) is found in serum, and plays an important role in the modulation of plasma lipids and lipoproteins levels. Inhibition of CETP can elevate the HDL-C level and decrease the LDL-C level, and may be considered as a novel strategy for reducing CVD risk. In one clinical study, patients with metabolic syndrome taking crocin supplements had significantly decreased CETP and increased HDL levels (Javandoost et al., 2017).

Other proposed mechanisms for the lipid-lowering effects of saffron may be the inhibition of pancreatic lipase activity, reduced absorption of fat and cholesterol, and a decrease in lipoprotein oxidation.
Safranal is the major contributor to the hypotensive activity of saffron. A high dose of saffron (400 mg) significantly decreased the systolic blood pressure of healthy subjects, as well as reducing their mean arterial pressure (Modaghegh et al., 2008).

In another clinical study, there was a significant reduction in the levels of total cholesterol and triglyceride (compared to baseline value) after six weeks supplementation of saffron (standardized for crocin) in patients with metabolic syndrome (Kermani et al., 2017).

As early as 1998, Verma and Bordia observed a significant decrease in the oxidation of LDL particles in patients with coronary artery disease after administration of 50 mg saffron, given in milk, twice a day. They surmised that saffron was able to improve CVD due to its potent antioxidant properties.

A meta-analysis of ten studies comprising over 600 patients showed significant reduction in diastolic pressure, body weight and waist circumference in the saffron group (Pourmasoumi et al., 2019).

**Antioxidant and Anti-inflammatory Effects**

Saffron’s active components – crocetin, crocins and safranal – are mainly responsible for both the antioxidant and anti-inflammatory properties, which contribute to increased protection against a variety of reactive oxygen and nitrogen species as well as against proinflammatory cytokines.

Numerous studies have confirmed that crocin and crocetin, the carotenoid constituents of saffron, showed high radical scavenging activities, followed by safranal. This is likely due to their ability to donate a single hydrogen atom to the free radicals.

Several studies have confirmed the anti-inflammatory effects of saffron’s various bio-actives due to their significant inhibitory effects against cyclooxygenase 1 and 2 enzymes (COX1 and 2) and prostaglandin E2 production, and suppressing inflammatory genes expression via raising histone deacetylase activity.
**Sexual Health**
For centuries, saffron has been touted as an aphrodisiac. Studies examining the effects of saffron supplementation on sexual function have shown varied results. Modabbernia et al. (2012) found that four weeks administration of saffron (30 mg/day) was effective in treating fluoxetine-related erectile dysfunction. The side-effects of saffron were comparable to placebo, which is important because there can be significant and potentially serious side-effects with drug treatments for sexual impairment caused by taking a selective serotonin reuptake inhibitor (SSRI), and some may even reverse SSRIs effect on mood. However, studies of sexual dysfunction from other causes did not show that saffron was beneficial; for example, compared to placebo in infertile men with idiopathic oligoasthenoteratozoospermia (Safarinejad et al., 2011), and compared to sildenafil in men with erectile dysfunction (Safarinejad et al., 2010).

Additionally, Kashani et al. (2013) conducted a study of women with major depression stabilized on fluoxetine who experienced subjective feelings of sexual dysfunction. Those randomly assigned to take saffron (30 mg/day) compared to placebo reported significant improvements in sexual function.

It is likely that saffron may be effective for sexual dysfunction associated with antidepressants (e.g., Fluoxetine), but otherwise its aphrodisiac properties are unfounded.

**Premenstrual Syndrome**: Agha-Hosseini et al. (2008) studied the effects of saffron (30 mg/day) on premenstrual syndrome (PMS) and found that women reported relief of PMS symptoms and depression levels compared to placebo.

**Menopausal symptoms**: Kashani et al. (2018) studied the use of standardized saffron extract in reducing hot flashes in post-menopausal women and reported significant reduction of symptoms compared to placebo.

**SUMMARY**
With over 150 identified compounds in this highly prized herb, saffron has widespread traditional health-related uses, from reducing inflammation to PMS relief. The growing body of research on saffron is confirming its therapeutic role in improving mood and anxiety, balancing homocysteine levels and more. It is a natural support for neurotransmitters, which modulate various functions including mood and sleep. Studies to date support its effective role in the management of depressive symptoms, with mechanisms of action thought to be similar to prescription antidepressants. Saffron has also been found to have GABA-like effects, which assists in relieving feelings of anxiety. Saffron has been clinically proven to help manage stress while supporting mood balance, and scientific studies continue to reveal its other health-related advantages.
REFERENCES


REFERENCES (cont).

### APPENDIX 1. LIST OF STUDIES ON SAFFRON IN DEPRESSION/ANXIETY.

<table>
<thead>
<tr>
<th>Population group</th>
<th>Severity of depression</th>
<th>Saffron administration</th>
<th>Comparison</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with MDD and anxiety</td>
<td>moderate</td>
<td>30 mg/day (15 mg saffron extract/capsule)</td>
<td>Citalopram</td>
<td>Effective similar to citalopram</td>
<td>Ghajar 2017</td>
</tr>
<tr>
<td>Patients with depression and anxiety</td>
<td>mild to moderate</td>
<td>100 mg/day (50 mg dried stigma/capsule)</td>
<td>Placebo</td>
<td>Significant effect on BDI/BAI scores compared to placebo</td>
<td>Mazidi 2016</td>
</tr>
<tr>
<td>Adult outpatients with depression</td>
<td>moderate</td>
<td>30 mg/day (15 mg ethanolic (80% ethanol) extract of the petal/capsule)</td>
<td>Fluoxetine</td>
<td>Effective similar to fluoxetine</td>
<td>Akhondzadeh Basti 2007</td>
</tr>
<tr>
<td>Adult outpatients with depression</td>
<td>moderate</td>
<td>30 mg/day (15 mg ethanolic (80% ethanol) extract of the petal/capsule)</td>
<td>Placebo</td>
<td>Significantly better outcome than placebo</td>
<td>Moshiri 2006</td>
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<td>moderate</td>
<td>30 mg/day (15 mg ethanolic (80% ethanol) saffron extract/capsule)</td>
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<td>Significantly better outcome than placebo</td>
<td>Akhondzadeh 2005</td>
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<td>Adult outpatients with depression</td>
<td>moderate</td>
<td>30 mg/day (15 mg ethanolic (80% ethanol) saffron extract/capsule)</td>
<td>Fluoxetine</td>
<td>Effective similar to fluoxetine</td>
<td>Noorbala 2005</td>
</tr>
<tr>
<td>Adult outpatients with depression</td>
<td>mild to moderate</td>
<td>30 mg/day (TDS) (15 mg ethanolic (80% ethanol) saffron extract/capsule)</td>
<td>Imipramine</td>
<td>Effective similar to imipramine</td>
<td>Akhondzadeh 2004</td>
</tr>
<tr>
<td>Adult patients</td>
<td>BDI scale of depression</td>
<td>100 mg/day</td>
<td>Placebo</td>
<td>BDI score deceased about 2x that of placebo group</td>
<td>Shemshian 2011</td>
</tr>
<tr>
<td>Medical students</td>
<td>BDI scale of depression</td>
<td>Drank tea containing saffron 3 times/day</td>
<td>Pre-Test Post-Test</td>
<td>Decreasing of mean score</td>
<td>Masinaei Nezhad 2005</td>
</tr>
<tr>
<td>Heart patients with MDD who underwent PCI</td>
<td>mild to moderate</td>
<td>30 mg/day (15 mg saffron extract/capsule)</td>
<td>Fluoxetine</td>
<td>Effective similar to fluoxetine</td>
<td>Shahmansouri 2014</td>
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<tr>
<td>Patients with coronary artery disease</td>
<td>moderate</td>
<td>30 mg/day (15 mg saffron extract/capsule)</td>
<td>Placebo</td>
<td>Significant decrease in BDI scores</td>
<td>Abedimanesh 2017</td>
</tr>
<tr>
<td>Patients with MetS and depression</td>
<td>BDI scale of depression</td>
<td>30 mg of crocin (15 mg/tablet)</td>
<td>Placebo</td>
<td>Significantly better outcome than placebo</td>
<td>Jam 2017</td>
</tr>
<tr>
<td>Women (20-45 y) with regular menstrual cycles and PMS at least 6 months</td>
<td>HAM-D scale of depression</td>
<td>30 mg/day (15 mg twice a day)</td>
<td>Placebo</td>
<td>Effective in relieving symptoms of PMS, including depression</td>
<td>Agha-Hosseini 2008</td>
</tr>
<tr>
<td>Women (18-45 y) with post-partum depression</td>
<td>mild to moderate</td>
<td>30 mg/day (15 mg saffron extract/capsule)</td>
<td>Fluoxetine</td>
<td>Effective similar to fluoxetine</td>
<td>Kashani 2017</td>
</tr>
<tr>
<td>Breastfeeding mothers with post-partum depression</td>
<td>mild to moderate</td>
<td>30 mg/day (15 mg saffron/ tablet)</td>
<td>Placebo</td>
<td>More significant impact on the BDI scores than placebo</td>
<td>Tabeshpour 2017</td>
</tr>
<tr>
<td>Post-menopausal women with MDD associated with hot flashes</td>
<td>mild</td>
<td>30 mg/day (15 mg saffron extract/capsule)</td>
<td>Placebo</td>
<td>Significant reduction of symptoms compared to placebo</td>
<td>Kashani 2018</td>
</tr>
</tbody>
</table>

BDI, Beck Depression Inventory; BAI, Beck Anxiety Inventory; HAM-D, Hamilton Depression Scale; HAM-A, Hamilton Anxiety Scale; MDD, major depressive disorder; MetS, metabolic syndrome; PCI, percutaneous coronary intervention; PMS, premenstrual syndrome