



SafraSOL™

The condiment that helps
to improve your mood



APPLICATIONS

SafraSOL™ is an ingredient that can be used in different situations that affect the nervous system, so it is recommended for:

- Improve well-being (behavior and mood).
- Depression
- Memory loss
- Parkinson
- Neuronal Inflammation

INTRODUCTION

Saffron (*Crocus sativus* L.) is a small plant with six blue petals and three stigmas that are highly appreciated in many traditional cuisines, being used as a natural flavouring and colouring. The fact that the flower contains only three stigmas and the laborious system of harvesting makes the price of this ingredient very high, since to obtain 1 g of roasted stigmas it is needed among 150 and 200 flowers and more than 200,000 are necessary to obtain 1 kg of saffron, which can reach 3000 euros per kg.

A part from its culinary properties, saffron has also been used traditionally in Asia as a medicinal plant with sedative, antispasmodic, aphrodisiac, diaphoretic, expectorant, stimulant, anti-inflammatory, antioxidant and emenagogue properties and for the treatment of premenstrual syndrome.

Originally from Asia, this plant is grown mainly in Iran (the main world producer), Afghanistan, Turkey and Spain and contains more than 150 different compounds in its stigmas, among which are carotenoids and

different glycosides responsible for their healthy properties. Some of the carotenoids present in saffron are crocins (being crocin 80% of total pigments and the main responsible for the colouring capacity of saffron), crocetin, alpha and beta-carotene, lycopene and zeaxanthin, but also contains a significant amount of riboflavin that also helps giving colouring capacity.

Crocins represent 6 to 16% of the total dry weight of saffron. They are easily soluble in water, although to be absorbed they must first be hydrolysed in the gut producing crocetin, which is well absorbed through the intestinal mucosa.

Saffron stigmas also contain picrocrocina, a bitter principle that, when hydrolysed, is transformed into safranal, the main aromatic component present in the essential oil. However, unlike crocins, safranal is not water-soluble.

All these compounds behave like active principles when concentrated in saffron extracts that can contain different concentrations of crocetin, crocins and safranal.

Pharmacological activity

Among other actions, crocins and safranal stand out for their antioxidant, anti-inflammatory, tissue oxygenating, lipid-lowering and hepatoprotective properties. Specifically, crocetin has demonstrated its ability to reduce serum cholesterol levels with a positive impact on the prevention of atherosclerosis.

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Crocin, at very low concentrations, and safranal have an important free radical scavenger activity. In addition, crocin has hepatoprotective action against the damage caused by aflatoxin B1 and dimethylnitrosamine, a derivative of nitrosamine formed at high temperatures, for example, in frying foods, but also in products that use nitrites as preservatives.

In animal experimental models, safranal has demonstrated its capacity to stimulate sexual activity. This compound stimulates β 2-adrenergic receptors and blocks muscarinic and histamine receptors, which manifests itself in a relaxing action on muscular and nervous system.

The analysis of the active fractions of saffron have revealed that crocin is the main responsible for the antidepressant effect. The antidepressant effect manifests itself in the first week, obtaining the maximum effect approximately six weeks after the start of consumption.

In addition, the active principles of saffron extract have a neuroprotective action against ischemic damage. Several studies have shown that crocin inhibits lipid peroxidation and restores the activity of superoxide dismutase (SOD) and glutathione peroxidase, maintaining the morphology of neurons. This action could prevent the damage caused by ischemic phenomena and oxidative processes associated to them in the brain, that affect the spatial learning and memory processes carried out in the hippocampus.

On the other hand, the beneficial effects of saffron on neurodegenerative disorders such as Alzheimer's and Parkinson's disease are mainly due to their interactions with the cholinergic, dopaminergic and glutamatergic systems. The aqueous extract of saffron increases the concentration of neurotransmitters such as dopamine and glutamate in the brain in a dose-dependent manner.

The anticonvulsant and analgesic properties of saffron, as well as its effects on morphine withdrawal, could be due to an interaction between the active compounds of saffron, gamma-aminobutyric acid (GABA) and the opioid system.

The antioxidant and anti-inflammatory effects of saffron extracts and their components crocetin, crocins and safranal imply a therapeutic potential of saffron for the treatment of various nervous disorders.

SAFFRON AT THE LEVEL OF NERVOUS SYSTEM

Meta-analysis: efficacy of saffron in the treatment of mild to moderate depression

Eleven randomized double-blind trials were included in a meta-analysis published in 2019 for its qualitative analysis. Nine of them pooled for statistical analysis.

Saffron scientific literature was review and the meta-analysis tried to synthesize the currently available published evidence on the antidepressant efficacy of saffron, as well as to assess the safety profile of this plant based on the included trials.

All the included clinical trials, from 2004 until 2018, were conducted in Iran, where saffron is easily accessible.

The eleven randomized trials included more than 500 patients, 256 of whom received saffron. Available data from these clinical trials supported that saffron was significantly more effective than placebo, and non-inferior to tested antidepressant drugs.

In all the studies, the daily dosage of saffron extract was 30 mg except in only one that was 100 mg. Some trials were carried out with commercially available products.

One of the available commercial products was supplied in capsules containing 15 mg saffron dry extract standardized to crocin supplying 1.65-1.75 mg crocin per capsule. Other product was also supplied in capsules but, in this case, was standardised in safranal supplying 0.30-0.35 mg safranal per capsule. Finally, other of the available commercial saffron products was administered in tablet giving 5 mg crocin per tablet.

Not all the studies confronted saffron versus placebo. Six randomized controlled trials compared the antidepressant efficacy of saffron versus accepted antidepressant drugs.

For comparison:

- Five trials used SSRI (Selective Serotonin Reuptake Inhibitor):
 - Four of them used **fluoxetine** (PROZAC)
 - One used **citalopram**
- One trial used tricyclic antidepressant **imipramine**.

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Antidepressants generally seem to be more effective than saffron, but the result of our meta-analysis failed to show a significant difference between saffron and SSRIs.

Finally, the incidence of the reported adverse reactions was not significantly different from that associated with placebo. However, patients who received imipramine experienced sedation and dry mouth significantly more often than patients in the saffron group.

The conclusion of this meta-analysis is that **saffron (*C. sativus*) was safe and statistically significantly superior to placebo in the treatment of mild to moderate depression, and non-inferior to antidepressants.** (figure 1)

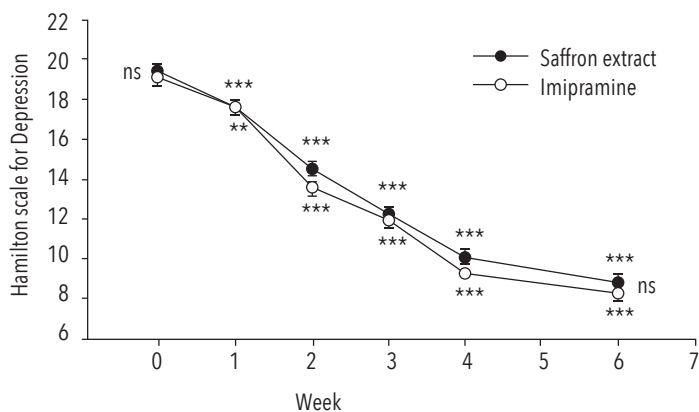


Figure 1. Scores of the two groups of patients according to the Hamilton rating scale for Depression ns = not significant, ** = P <0.01 and *** = P <0.001. The horizontal symbols (** and ***) indicate significant difference respect to the values of the beginning and the symbols ns are the comparisons between groups.

Effect on senile dementia, memory loss and Parkinson's

Alzheimer's disease is a degenerative pathology of the central nervous system whose origin is the deposition of beta-amyloid peptide plaques in the brain caused by oxidative processes.

Studies with saffron extracts have shown that, in a dose-dependent manner, crocins inhibit the formation of insoluble amyloid plaques.

It has also been shown that saffron extracts produce a cognitive improvement through a moderate effect on the inhibition of acetylcholinesterase

(AChE). The inhibition of this enzyme allows maintaining the concentration of acetylcholine at the level of the neuronal synapse, which is one of the mechanisms of action presented by the drugs used in the treatment of senile dementia of Alzheimer's type.

Concerning this disease, there were published two clinical studies in patients suffering from Alzheimer's disease treated with saffron. The **first study** involved 46 patients affected with senile dementia who were treated for 16 weeks with saffron or placebo. At the end of the treatment, the patients of the saffron group showed an improvement of the cognitive functions with respect to the placebo group.

The **second clinical trial** was a randomized multicenter 22-week donepezil-controlled study involving 54 patients aged 55 years and older with mild to moderate Alzheimer's disease. Patients were divided into two groups. One group received a daily dose of 30 mg of saffron extract, shared into two capsules of 15 mg of extract each, while the other group was treated with 10 mg of donepezil. The content of active components in this saffron extract was evaluated using spectrophotometry. The analysis showed a range of 0.13-0.15 mg of safranal and 1.65-1.75 mg of crocin per capsule.

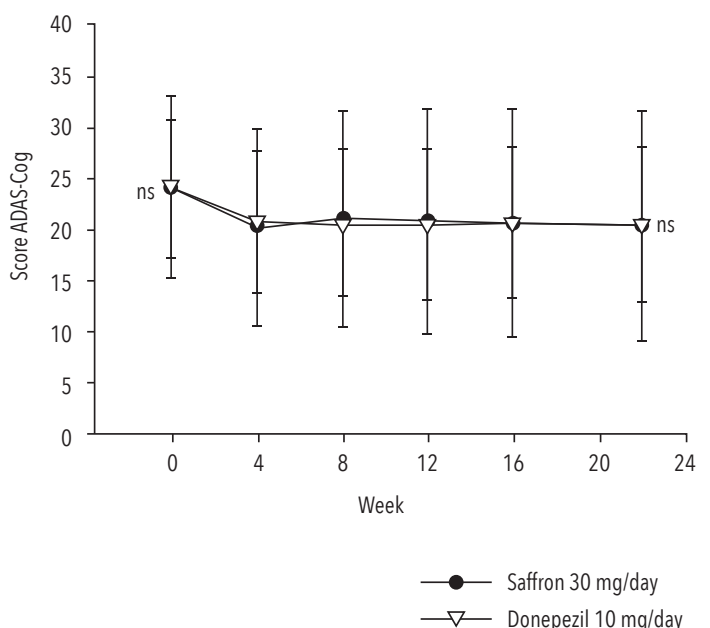


Figure 2. Score on the ADAS-cog assessment scale of the results with the treatments of saffron (30 mg / day) and donepezil (10 mg / day) in patients with senile dementia of the Alzheimer's type. ns = not significant

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The results of this clinical trial showed that the treatment with the saffron extract was as effective as donepezil drug (Figure 2), but without producing cases of vomiting, which is the most frequent side effect associated with this medication.

From these studies, it is clear that saffron, as well as its main active ingredients safranal and crocin, can help in the treatment of Alzheimer's disease and other neurodegenerative diseases, especially in relation to memory loss.

In traditional Iranian medicine, saffron has been used for its anticonvulsant properties for treatment of Parkinson's disease. This action has also been demonstrated in animal experiments, in which the use of saffron extracts has reduced the antiepileptic activity induced in the animal. Safranal is the active principle responsible for the delay in the onset and duration of seizures, probably by modification of the binding site for benzodiazepines in the GABAA receptor complex.

As demonstrated in Alzheimer disease, crocin and safranal have been shown in experimental animal models to have an inhibitory effect on the formation of toxic amyloid structures related to neurodegeneration in Parkinson's disease. The possible mechanism of action could be explained by the protective effect of dopaminergic cells of the central nervous system.

SAFRASOL™

SafraSOL™ is an extract of saffron standardized to 10% in crocins and to 2% in safranal. This extract has been prepared keeping the two main active principles responsible for the activity of saffron at the level of the nervous system.

SafraSOL™ contains also picrocrocin that gives the typical aromatic smell of saffron.

This extract of saffron is soluble in water, although some precipitate may appear as a consequence of the presence of the excipient used in the extract, as well as other typical saffron compounds remaining in the extract.

DOSAGE

According to clinical studies carried out with saffron extracts in the treatment of diseases of the nervous system, a dosage of 30 mg of SafraSOL™ per day divided into two doses of 15 mg is recommended.

This 30 mg of SafraSOL™ provides 3 mg of crocins (approximately 2.4 mg of crocin) and 0.6 mg of safranal.

SAFETY

Saffron is a safe condiment and there are no known contraindications except in cases where the person is allergic to it.

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