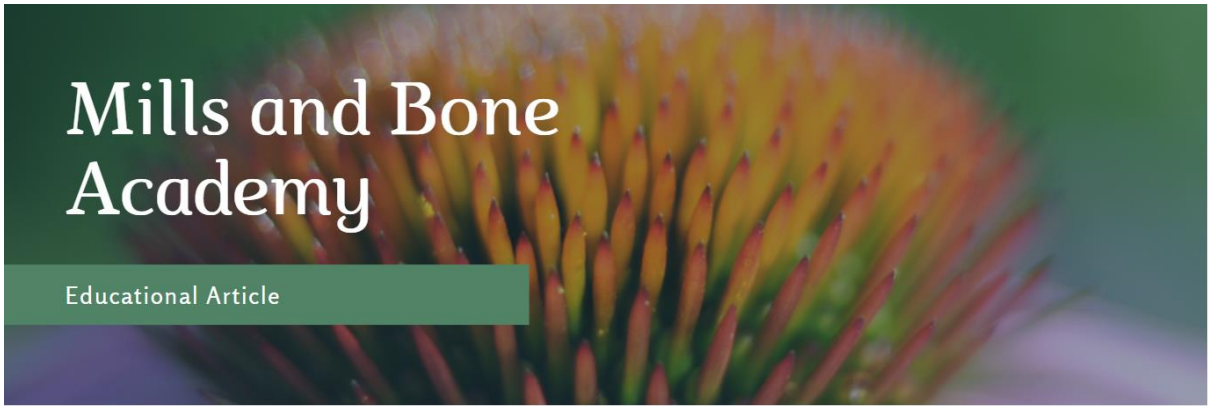

Saffron: An Impressive Range of Health Benefits from this Age-old Spice – Kerry Bone

Saffron (*Crocus sativus*) is the world's most expensive spice. That's because it is still hand-harvested from the beautiful lilac-purple flowers of a small low-growing crocus. Each flower yields only three small threadlike stigmas that are bright orange-red and form the spice as we know it. This intense orange-red colour comes from an extraordinarily high content of carotenoid molecules, mainly the crocins. When we consume saffron, the crocins release the carotenoid crocetin into our bloodstream. In a sense, the saffron stigma is a super-concentrated source of highly bioavailable carotenoids, with health-promoting properties similar to, but unique from, other key carotenoids such as astaxanthin and lutein.

I first wrote about the new clinical research on saffron in this journal five years ago. In that article I outlined the results of 5 clinical trials where saffron was shown to be more effective than placebo at alleviating depression[i,ii] and just as active as conventional drugs, including fluoxetine (Prozac).[iii,iv,v]

More positive news in depression

Since that article, many more trials demonstrating a diverse range of health benefits for saffron have been published. In the case of depression, there have been two new trials that looked at the effect of combining saffron with fluoxetine in depressed patients suffering from sexual dysfunction as a side effect of the drug. The first trial tested the influence of saffron on fluoxetine-induced sexual dysfunction in men.[vi] This was a 4-week randomised, double blind, placebo-controlled study. Thirty-six married male patients with major depressive disorder whose depressive symptoms had been stabilised on fluoxetine and had subjective complaints of sexual impairment entered the study. The patients were randomly assigned to saffron extract (15 mg twice per day) or placebo for 4 weeks. The International Index of Erectile Function scale was used to assess sexual function at baseline and weeks 2 and 4.

Thirty patients finished the study. Baseline characteristics as well as baseline and final depressive symptoms scores were similar between the two groups. By week 4, saffron

resulted in significantly greater improvement in erectile function, intercourse satisfaction domains and total scores than the placebo group. Nine patients (60%) in the saffron group and one patient (7%) in the placebo group achieved normal erectile function (score >25 on erectile function domain) at the end of the study. The frequency of side effects was similar between the two groups.

In the second trial, the impact of saffron on fluoxetine-induced sexual dysfunction was assessed in women.[vii] Using a similar trial design to above, 38 women with major depression who were stabilised on fluoxetine 40 mg/day for a minimum of 6 weeks and had experienced subjective feelings of sexual dysfunction entered the study. The patients were randomly assigned to saffron extract (30 mg/daily) or placebo for 4 weeks. Measurement was performed at baseline, week 2 and week 4 using the Female Sexual Function Index (FSFI). Side effects were systematically recorded.

Thirty-four women had at least one post-baseline measurement and completed the study. At the end of the fourth week, patients in the saffron group experienced significantly greater improvement in total FSFI, and for the arousal, lubrication and pain domains of the FSFI. Frequency of side effects was similar between the two groups.

Safe to combine with conventional antidepressants

These new trials highlight an important advantage of saffron in depression; it appears to be quite safe to add to conventional antidepressant drugs. To date, there is only preliminary information as to the neurological pathways influenced by saffron. It appears on current evidence to have minimal impact on serotonin metabolism. Rather research attention is focused on the impact of its phytochemicals on NMDA (N-methyl-D-aspartate) and Sigma-1 receptors in the brain.[viii,ix] Saffron extracts and trans-crocetin demonstrated a clear binding capacity at the phencyclidine (PCP) binding site of the NMDA receptor and at the Sigma-1 receptor, whereas the crocins were not effective.[viii] The authors suggested that it can be assumed that the binding of saffron and crocetin to the NMDA receptor will lead to an antagonistic effect, because agents that attach to the PCP binding site block the channel pore of the NMDA receptor system. This could explain the antidepressant and other central nervous system effects of saffron. Moreover, excess neuron excitation caused by activating these receptors can lead to neuronal dysfunction or even cell death (excitotoxicity). Memantine, a drug used to treat Alzheimer's disease is an NMDA receptor channel blocker. Many central and peripheral effects are modulated by the mysterious Sigma-1 receptors, including possible activity in clinical depression and schizophrenia and for neuroprotection.[viii]

Follow-up work by the same research centre confirmed these results for an extract of saffron and trans-crocetin on postsynaptic NMDA receptors and demonstrated an inhibitory effect for saffron extract only on postsynaptic kainate receptors.[ix] Other researchers have found that saffron extract and safranal (a monoterpenoid essential oil component of saffron) interact with the $GABA_A$ receptor complex, thereby mediating anticonvulsant and potential anxiolytic activities.[x,xi]

The important message from the mechanistic studies is that saffron is highly unlikely to interact adversely with modern antidepressant drugs, especially selective serotonin re-uptake inhibitors (SSRIs). Specifically, there is little suggestion from current research that the herb substantially influences serotonin metabolism.

Saffron benefits the brain and women's health

Preliminary trials of saffron's impact on brain function are also promising. In a comparative trial in 54 people with moderate Alzheimer's disease, saffron stigma extract (30 mg/day) was as effective as the modern drug donepezil (10 mg/day) on cognitive functioning over 22 weeks.[xii] It was also more effective than placebo at the same dose in 46 patients with mild to moderate Alzheimer's over 16 weeks.[xiii]

The impact of saffron extends to women's health. Saffron stigma (30 mg/day of extract) over 2 menstrual cycles significantly relieved symptoms of premenstrual syndrome (PMS) in a double blind, placebo-controlled clinical trial.[xiv] Patients on saffron also had significantly better depression scores. A combination of saffron, celery and anise relieved dysmenorrhea (period pain) symptoms in a 3-arm placebo-controlled trial involving 180 women.[xv] The herbal combination actually worked better than mefenamic acid, a commonly used drug for this problem.

A new development in helping weight loss

Saffron seems to be a valuable discovery to reduce food craving and snacking, something we can all benefit from. Based on preclinical and clinical studies reporting positive anti-anxiety and antidepressant effects for saffron, a team of French scientists wondered if the herb might balance mood and reduce snacking and the desire to eat, making it a suitable supplement for people undertaking weight loss programs. To test this hypothesis a placebo-controlled, randomised clinical trial was done using a proprietary extract of saffron stigma in 60 healthy women who were mildly overweight (body mass index (BMI) 25 to 28 kg/m^2).[xvi] Over 8 weeks the participants consumed one capsule of saffron extract (exact details not provided, but probably corresponding to 100 to 150 mg of original stigma) twice a day or a matching placebo. Caloric intake was left unrestricted during the study.

Saffron treatment resulted in a significantly greater body weight reduction than placebo. But the main result was a striking reduction in weekly snacking events with saffron (reduced from 6.1 to 2.9) compared to the placebo group (reduced from 6.3 to 4.5). This was evaluated only in those women who exhibited 'snacking' behaviour (16 in each trial group). Saffron also scored significantly higher for the questions: "Did you feel less hungry before meals?" and "Did the product help reduce your need for snacking between meals?". There were no differences between the saffron and placebo groups in terms of tolerance, and the noted side effects were mild and transient.

A super-carotenoid for the eyes

Finally, as you might expect given its high levels of carotenoids, saffron is showing promise in eye health, especially for the retina. The influence of saffron on retinal health was first clinically investigated by researchers from

Italy and Australia in a double blind trial that was reported in December 2010. Twenty-five patients with early age-related macular degeneration (AMD) were randomly divided into two groups, either taking saffron or placebo for a period of 90 days. The groups were then crossed over to receive the other treatment, with a washout period of 15 days between them.[xvii] Patients took saffron at a daily dose of 20 mg of powdered dried stigma. Very low, sub-therapeutic doses of turmeric, black pepper and DHA were also present in the tablets.

Retinal flicker sensitivity was assessed. Flicker sensitivity, evaluated by the focal electro-retinogram, provides an estimation of the macular dysfunction in age-related macular degeneration, because it analyses the functioning of the cones in the retina. From each patient, one eye, typically the eye with the best visual acuity (sharpness of vision), was selected and designated as the study eye.

Daily intake of saffron for 90 days was associated with a significant improvement in retinal function. No changes were observed in the same patients after administration of placebo. There was also a small but statistically significant increase in average visual acuity after taking saffron.[xvii] (A calibrated standard Snellen chart was used to evaluate visual acuity, and means for example, that a number of patients were able to read one or two lines on the eye chart that were smaller than the lines they could read before treatment with saffron.[xviii])

The same research team conducted further research with the aim of finding out whether the benefits observed from saffron treatment would extend over a longer duration. Twenty-nine patients with early AMD were recruited from an outpatient eye clinic.[xix] As was the case with the previous study, the patients were not taking medications known to affect macular function or to interfere with carotenoid absorption. They received ongoing treatment with the same saffron tablet described above (providing 20 mg/day powdered dried stigma). Two patients completed 6 only months of treatment, with 7 and 20 patients completing 12 and 15 months.

Compared to the start of the trial, after 3 months of treatment retinal function improved and the mean visual acuity improved by two Snellen lines with saffron. These results were statistically significant and remained stable over the treatment period (6 to 15 months). In addition, all the patients volunteered an improvement in their quality of vision, most commonly reporting an improvement in contrast and colour perception, reading ability and vision in low light. Perhaps because of these improvements, everyone indicated an enhancement in their quality of life.

How much to take?

As mentioned above, saffron is very expensive, but fortunately it is so highly concentrated in carotenoids that effective clinical doses are not high, helping to keep the cost down. The trials in AMD used just 20 mg of dried stigma per day. Most of the other trials used 30 mg/day of a concentrated extract, probably corresponding to around 180 mg/day of stigma.

Acknowledgment

Thanks to Michelle Morgan for contributing to this review.

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