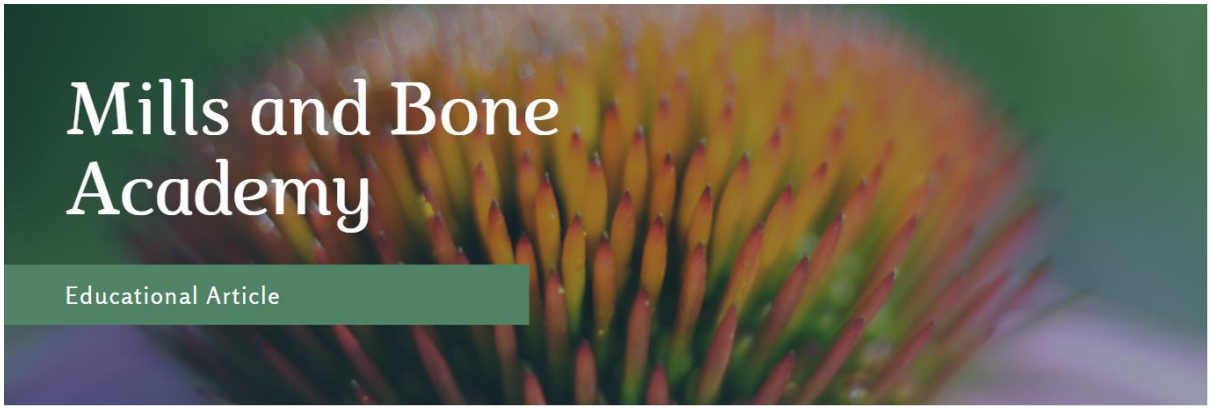

Herbs for Depression: Recent Developments – Kerry Bone

Herbs with antidepressant activity form part of the herbal category known as the nervine tonics (or nervous system trophorestoratives). The best known example is St John's wort *(Hypericum perforatum)*, which unfortunately has acquired the reputation of interacting adversely with antidepressant drugs.

In addition, there is some encouraging research that has highlighted some unlikely herbal candidates for antidepressant activity, namely Bupleurum *(Bupleurum falcatum)* and saffron *(Crocus sativus)*. Also, perhaps not unexpectedly, the tonic herb Rhodiola now has some reasonable evidence for a supporting role in depression.

This article reviews some of the recent developments for these herbs in depression, with an emphasis on the results from clinical trials.

Saffron and mood: now a significant player

There have been several controlled clinical trials investigating the impact of a saffron extract on mood in depressed patients (including the diagnosis of major depressive disorder, MDD). Now a group from the United States has subjected the results of those clinical trials of saffron in MDD to a meta-analysis.[i] Based on the authors specified selection criteria, five randomised, controlled trials (RCTs) (two placebo controlled trials and three antidepressant-controlled trials) were included in the review. A large effect size was found for saffron supplementation versus placebo in treating depressive symptoms ($p < 0.001$), revealing that saffron significantly reduced depression symptoms compared to the placebo control. A null effect size was seen between saffron supplementation and the antidepressant drugs, suggesting that both treatments were similarly effective in reducing depression symptoms. The mean Jadad score was 5, indicating a high quality for the trials. The authors concluded that the findings from clinical trials published to date indicate saffron supplementation can improve symptoms of depression in adults with MDD. They suggested larger and longer clinical trials conducted by international research teams are needed before firm conclusions can be made.

Since that meta-analysis, there has been an additional trial in a special cohort.[ii] A significant correlation exists between coronary artery disease and depression, hence the aim of the trial was to compare the efficacy and safety of saffron versus fluoxetine in improving symptoms in patients who were suffering from depression after receiving percutaneous

coronary intervention (PCI, coronary angioplasty). In this small randomised, double blind, parallel-group study, 40 patients with a diagnosis of mild to moderate depression who had undergone PCI in the last six months were randomised to receive either fluoxetine (40 mg/day) or saffron extract (30 mg/day) for six weeks. Participants were evaluated by Hamilton depression rating scale (HDRS) at weeks 3 and 6 and any adverse events were recorded. By the study endpoint, no significant difference was detected between two groups in terms of reduction of HDRS scores ($p = 0.62$). Remission and response rates were not significantly different as well ($p = 1.00$ and $p = 0.67$; respectively). Also there was no significant difference between the two groups in frequency of adverse events during the trial.

As some indication of what might be active in saffron, the carotenoid compound crocin (a major component that contributes to its intense yellow/orange colour) has also been investigated as an adjunctive treatment in MDD.[iii] This study was a placebo-controlled, pilot RCT over 4 weeks in 40 MDD patients. The crocin group ($n = 20$) was given one selective serotonin reuptake inhibitor (SSRI) drug (fluoxetine 20 mg/day or sertraline 50 mg/day or citalopram 20 mg/day) plus crocin tablets (30 mg/day). The placebo group ($n = 20$) was administered one SSRI (fluoxetine 20 mg/day or sertraline 50 mg/day or citalopram 20 mg/day) plus placebo (two placebo tablets per day). Both groups completed Beck depression inventory (BDI), Beck anxiety inventory (BAI), a general health questionnaire (GHQ), the mood disorder questionnaire (MDQ), a side effect evaluation questionnaire, and a demographic questionnaire before and after one month of intervention. The crocin plus SSRI drug group showed significantly improved scores on BDI, BAI and GHQ compared to the placebo plus SSRI drug group ($p < 0.0001$). The mean decreases in BDI, BAI and GHQ scores in the SSRI plus placebo group were 6.15, 2.6 and 10.3 respectively; whereas corresponding values in the SSRI plus crocin group were 17.6, 12.7 and 17.2 by the end of the 4-week trial. The study was hampered by poor patient compliance with medications and a short trial period.

Although the trial immediately above was using crocin and not saffron, it does suggest the herb is safe with conventional SSRIs. Such a conclusion is also backed up by trials of saffron in men and women with sexual dysfunction while taking SSRIs.[iv] This is further supported by experimental data that saffron's neurotransmitter impact is more likely to be at NMDA (N-methyl-D-aspartate) and Sigma-1 receptors in the brain, rather than serotonin receptors.

There are other possible mechanisms of action for saffron in depression. These were recently reviewed by an Australian team, who first conducted a systematic review of clinical trials.[v] From this 2014 review, the authors concluded the clinical trials conducted so far provide initial support for the use of saffron in mild to moderate MDD. In terms of mechanisms, they highlighted saffron's antidepressant effects are potentially due to its antioxidant, anti-inflammatory, neuroendocrine and neuroprotective effects. The authors also suggest a possible serotonergic effect, but concede the evidence here is very limited (confined to one rodent study not using a depression model).

Consistent with these proposed mechanisms for saffron, two other key hypotheses (besides the neurotransmitter hypothesis) of what possibly underlies depressive illness are receiving increasing research attention: neuroinflammation (with associated increased oxidative stress, decreased neuronal plasticity

and mitochondrial dysfunction) and dysregulation of hypothalamus-pituitary-adrenal (HPA) axis function.[v] As noted briefly above, the Australian review suggests that saffron could be acting to correct these pathophysiologies, rather than having any direct impact on serotonin neurotransmitter function (or perhaps in conjunction with a mild effect on serotonin neurotransmission that would not create any interactive risk with SSRIs).

Rhodiola: active and less side effects than sertraline

The first clinical study of Rhodiola in depression was a 6-week RCT (n=99), published in 2007. Two doses of the herbal extract (340 or 680 mg/day) were compared against a matched placebo. Results revealed that depression, insomnia and emotional instability all improved in both Rhodiola groups.[vi]

More recently there has been a 12-week RCT (n=57), where Rhodiola extract (340 mg/day) was compared with the drug sertraline (50 mg/day) or a placebo. The Rhodiola extract was active compared to the placebo, but less so than drug. However, the herb did show fewer side effects.[vii]

The postulated mechanism for Rhodiola in depression via animal models is improved sensitivity of the glucocorticoid receptor (GR) via a downregulation of stress-activated protein kinases (SAPK).[viii] SAPK, also known as JNK, are released in response to stress and pro-inflammatory cytokines**.** They are thought to play a key role in in the links between HPA axis overactivity, neuroinflammation and depression.

A surprising result for Bupleurum

Chinese herb Bupleurum has been regarded in China as effective to improve depression, but the mechanism of action remains unknown. Low levels of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) increase the likelihood of developing the depression, although their role is controversial. Recently a group of Chinese researchers investigated whether Bupleurum could help depression in a clinical trial setting, and whether it did so by increasing these factors.[ix]

A total 160 haemodialysis patients diagnosed with depression were randomly assigned to two groups: Bupleurum (1 g root power in a capsule daily) and a control group (placebo). After a three-month follow-up the patients who received Bupleurum were found to have an improvement in depression symptoms, anxiety symptoms and general functioning, versus the control group ($p < 0.05$). Serum NGF levels were significantly higher in the patients taking Bupleurum (178.64 ± 52.18 pg/mL) when compared to control patients (103.54 ± 31.23 pg/mL) ($p < 0.01$). Similarly, serum BDNF levels were significantly higher for Bupleurum (1635.26 ± 121.66 pg/mL) versus the control group (516.38 ± 44.89 pg/mL) ($p < 0.01$). These serum levels of NGF and BDNF were negatively related with the Montgomery-Asberg Depression Rating Scale (MADRS) and positively related to a score of quality of life ($p < 0.01$). The authors concluded that the herb ameliorates depression by increasing serum levels of NGF and BDNF.

The surprising finding here was the huge increase in serum BDNF induced by Bupleurum; it was about triple the average in

the control group. Although this clinical study was in a special cohort (haemodialysis patients), the remarkable boost in BDNF suggests Bupleurum might have potential in other situations associated with reduced neuroplasticity, such as traumatic brain injury and brain ageing.

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