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File: ■ Saffron (*Crocus sativus*, Iridaceae)
■ Rhodiola (*Rhodiola rosea*, Crassulaceae)
■ Mild-to-Moderate Depression

HC 111855-618

Date: June 14, 2019

RE: Rhodiola and Saffron Combination Reduces Symptom Severity in Depression

Bangratz M, Ait Abdellah A, Berlin A, et al. A preliminary assessment of a combination of rhodiola and saffron in the management of mild–moderate depression. *Neuropsychiatr Dis Treat*. 2018:14:1821–1829. doi: 10.2147/NDT.S169575.

Conventional antidepressant medications are associated with incomplete response, low compliance, low remission rates, high risk of relapse, substantial side effects, low tolerability, and premature discontinuation. There is a need for alternative therapies, particularly for patients with mild-to-moderate depression. Clinical studies show that saffron (*Crocus sativus*, Iridaceae) dried stigmata and rhodiola (*Rhodiola rosea*, Crassulaceae) root individually have antidepressant effects. The authors hypothesize that a combination of saffron and rhodiola may be beneficial for treating depression. Hence, the purpose of this open-label observational study was to evaluate the effect of a fixed combination of saffron and rhodiola in patients with mild-to-moderate depression.

Patients (n = 59, aged 18–85 years) were recruited by general practitioners (GPs) in France who typically recommended dietary supplement to patients suffering from mild-to-moderate depression; in other words, these practitioners would have likely recommended alternative treatments regardless of study participation. The study was conducted from November 2016 to March 2017. Included patients had mild-to-moderate major depressive disorder (MDD) according to the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) diagnostic criteria and had a Hamilton Rating Scale for Depression (HRSD-17) score of 8–18. Excluded patients used antidepressants or discontinued antidepressants < 1 month prior to study entry; had severe MDD; attempted suicide or was suicidal; had other psychiatric disorders, such as schizophrenia, bipolar, or addiction; had a chronic disease; used medications containing piperine or St. John's wort (*Hypericum perforatum*, Hypericaceae) aerial parts; or were pregnant or lactating.

Patients were treated daily with 308 mg rhodiola extract and 30 mg saffron extract (Phytostandard de Rhodiole et Safran; PiLeJe Laboratoire; Paris, France) in two divided doses for six weeks. At baseline, week two, week four, and week six, the following assessments were conducted: HRSD-17 (the primary outcome measure), Clinical Global

Impression—Severity (CGI-S), Clinical Global Impression—Improvement (CGI-I), Hospital Anxiety and Depression Scale (HADS), Patient Global Impression of Change (PGIC) scale, safety, and compliance. Data for the intention-to-treat (ITT), modified ITT (mITT; patients who took at least one dose of the study medication and attended the second visit), and per protocol (PP) populations were analyzed. All patients who had received at least one dose of the supplement were included in the safety analysis.

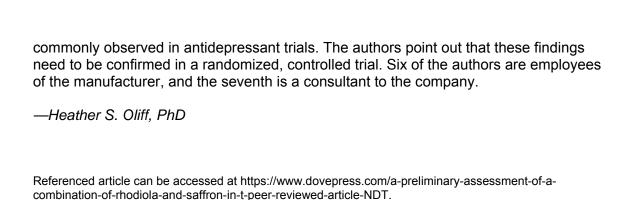
Of the 59 patients in the ITT, five were lost to follow-up, and nine did not meet the inclusion criteria, leaving 45 patients in the safety population. Four patients were discontinued from the study; three patients were erroneously included, and one was lost to follow-up. Therefore, the mITT population included 41 patients. Four patients were excluded due to poor compliance or use of unauthorized medications, leaving 37 patients in the PP population. The safety population (n = 45) was mostly women (82.2%), and the mean age was 47.6 years. The mean duration of the current depressive episode was 4.4 months. According to the HRSD score-classes, 53.7% of patients had mild depression, and 46.3% had moderate depression at baseline.

At week six, there was a significant 58% decrease in HRSD score compared with baseline, and 87.8% of patients had an HRSD score improvement of \geq 20%. The patients with the greatest improvement in HRSD had the greatest HRSD scores at baseline; HRSD scores decreased 53.7% in patients with mild depression and 62.9% in patients with moderate depression. Based on the change from baseline HRSD scores, 85.4% of patients improved, 12.2% of patients were stable, and 2.4% (1 patient) worsened. At six weeks, there was also a significant change in the patient distribution in the HDRS score-classes compared to baseline with 29 patients (70.7%) no longer suffering from depression and only two patients (4.9%) still suffering from moderate depression.

At six weeks, there was a significant 31.3% decrease in HADS anxiety and 46.1% decrease in HADS depression compared with baseline (P< 0.0001 for both). Significant improvements were seen as early as two weeks for HADS anxiety (P < 0.0001) and HADS depression (P < 0.05). A total of 71.8% of patients had an HADS anxiety score improvement of \geq 20%, and 66.7% of patients had an HADS depression score improvement of \geq 20%. CGI-S scores indicated that only six of the 41 patients (14.6%) were moderately or markedly depressed at six weeks compared to 31 patients (75.6%) at baseline (P < 0.0001). Overall, GPs deemed depression was significantly improved in 32 patients (78.1%). PGIC scores indicated that 56.4%, 62.5%, and 74.4% of patients reported feeling better after two weeks, four weeks, and six weeks, respectively. All significant results in the mITT analyses remained significant in the PP analyses.

Compliance was good; 76.9% of patients had no missed doses, and 23.1% missed a few days. Six patients (13.3%) reported nine adverse events (AEs). All AEs were mild and resolved. The AEs were dizziness (n =1), vision blurred (n = 1), arthralgia (n = 1), lower-abdomen pain (n = 1), dry mouth (n = 1), fatigue (n = 1), nausea (n = 1), and upper-abdomen pain (n = 2).

The authors conclude that six weeks treatment with the rhodiola and saffron fixed combination significantly decreased the severity of depression in patients diagnosed with mild-to-moderate depression, and the combination was well-tolerated. Acknowledged limitations of this pilot study include the relatively short treatment duration and more importantly, the lack of a placebo control group since a strong placebo effect is



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