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ORIGINAL RESEARCH

A preliminary assessment of a combination of rhodiola and saffron in the management of mild–moderate depression

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Objective: The medicinal plants *Rhodiola rosea* L. (rhodiola, golden root) and *Crocus sativus* L. (saffron) have been shown separately to induce significant effects in depression. The objective of this study was to assess a fixed combination of rhodiola and saffron in mild–moderate depression.

Methods: In this observational study conducted with general practitioners (GPs), 45 adults (aged 18–85 years) suffering from mild or moderate depression (International Statistical Classification of Diseases and Related Health Problems 10th Revision definition) and reaching a score on the Hamilton Rating Scale for Depression of 8–18 were supplemented with a combination of rhodiola and saffron extracts (one tablet, 154 mg of rhodiola and 15 mg of saffron; recommended dose two tablets per day for 6 weeks).

Results: After 6 weeks (D42) of supplementation, Hamilton Rating Scale for Depression scores (primary outcome) decreased significantly by 58%±28.5% (from 13.6±2.3 at D0 to 5.6±3.8 at D42, $P<0.0001$; n=41). Score improvement was reported in 85.4% of patients. A significant drop in both Hospital Anxiety and Depression Scale anxiety and depression scores was also observed at D42, the decrease being significant from 2 weeks of supplementation. At the end of the study, both GPs and patients deemed there was a significant improvement in depression (Clinical Global Impression – improvement and Patient Global Impression of Change). Safety was excellent, and no serious adverse effects were recorded.

Conclusion: Results of this observational study performed in primary care suggest that the combination of rhodiola and saffron tested could be useful for the management of mild–moderate depression and improve depressive and anxiety symptoms. A double-blind placebo-controlled study is needed to confirm these results.

Keywords: major depressive disorder, anxiety, *Rhodiola rosea*, *Crocus sativus*

Introduction

Depression is one of the most frequent and debilitating psychiatric conditions.[1–3] It has been reported that approximately one in five adults experiences at least one episode of depression in their lifetime, women being twice as likely to develop this disorder.[1,4] Depression is also widely underdiagnosed and undertreated, despite the wide range of treatments available.[1,2,4,5] It is estimated that <25% of depressive patients receive adequate treatment according to expert guidelines.[5,6] In addition, conventional antidepressants are often associated with incomplete response, low compliance, low remission rates, high risk of relapse, substantial side effects, low tolerability, and premature discontinuation.[1,6,7] Findings indicate that the efficacy of antidepressants varies considerably as a function of symptom severity.[6,8] It has been reported that whereas antidepressants can be quite potent with more severe depression, there is little evidence

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to suggest that they produce any benefit for the majority of patients with less severe forms of depression.[8] In addition, many patients with milder symptoms worry about side effects of antidepressants.[9] Certain guidelines for the management of depression recommend antidepressants for moderate–severe depression and not for mild depressive episodes, because the risk:benefit ratio is extremely poor. Psychological treatment, such as cognitive behavioral therapy, is recommended,[10–12] while other guidelines indicate either an antidepressant or psychotherapy (or both) in mild–moderate depression and both antidepressants and psychotherapy in severe or chronic forms of depression.[13,14] Psychological treatment, such as cognitive behavioral therapy, can be an effective alternative to pharmacotherapy.[15] However, since qualified therapists are rare and expensive, treatment access is quite low.[16] Therefore, there is a need for alternative or complementary medicines for less severe forms of depression to provide more favorable outcomes and easier access, especially since the majority of depressive patients suffer from mild–moderate forms of depression.[5]

Herbal medicines have been explored as a source for alternatives to conventional antidepressants, among which is saffron, a spice from the Middle East extracted from the flower of *Crocus sativus* L. Results of several preclinical studies and clinical trials have shown that saffron has beneficial effects in depression.[17–24] Supplementation with saffron was found to be as effective as treatment with conventional antidepressants, such as imipramine and fluoxetine, in randomized double-blind clinical trials.[17,19,23] Another plant with interesting properties is *Rhodiola rosea* L. (rhodiola, golden root), which is traditionally used to improve physical and mental performance and endurance.[25,26] Various extracts of rhodiola have been shown to produce interesting antidepressant effects in preclinical and clinical studies.[25,27–30]

On the assumption that supplementation with a combination of these two plants could be of benefit for depressive patients, we conducted an observational study in which a 6-week supplementation with a fixed combination of rhodiola and saffron extracts was evaluated in adults diagnosed with mild–moderate major depressive disorder (MDD). The study was performed in general practices, since depression is highly prevalent in primary care.[2]

Methods

Study design and ethics statement

This was an open-label, observational, longitudinal study performed in France between November 2016 and March 2017. The study was conducted in a context of routine practice: all measures were undertaken and supplement used in a usual way without any additional or unusual procedure of diagnosis or surveillance. The study was approved by the relevant French authorities for this type of study: the advisory committee on information processing in health research (Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé [CCTIRS]) and the National Commission on Informatics and Liberty. The study was performed in accordance with the ethical standards laid down in the Declaration of Helsinki and STROBE (strengthening the reporting of observational studies in epidemiology) guidelines. All patients received written information about the study and gave oral consent (approved by CCTIRS) before participation. The study was recorded on ClinicalTrials.gov site December 2016 (NCT02981225).

Participants and recruitment

Adult patients aged 18–85 years of either sex were recruited by general practitioners (GPs) used to recommending dietary supplement to patients suffering from mild and moderate depression: patients would have received the supplement regardless of whether or not the study were taking place. Patients had 1) to suffer from mild or moderate MDD according to the ICD10[31] and to have a Hamilton Rating Scale for Depression (HRSD) score of 8–18 (17 items).[32] Exclusion criteria were patients using an antidepressant or having discontinued it less than a month ago, severe MDD defined by the ICD10 or HRSD score >18, having attempted suicide or suicidal (based on the GP's opinion or HRSD item 3>2), psychiatric disorders, such as schizophrenia, bipolarity, and addiction, using chronic treatments (arterial hypertension, cardiac or renal insufficiency, for example), using medications containing piperine or St John's Wort (risk of interaction), and pregnant or lactating women.

Supplementation

The dietary supplement was a combination of rhodiola and saffron extracts (Phytostandard de Rhodiole et Safran; PiLeJe Laboratoire, Paris, France) marketed in France since 2015. One tablet contains 154 mg of an extract of rhodiola (*R. rosea* L., roots) and 15 mg of an extract of saffron (*C. sativus* L., stigmas). The supplement was recommended to be taken at the dose of two tablets per day for 6 weeks.

Procedure

The procedure was compliant with routine practice and the official recommendations for the management of depression.[33] On the first visit (V1, day 0 [D0]), eligibility of patients was

checked. GPs completed an electronic inclusion form with sociodemographic and anthropometric characteristics (age, sex, height, and weight), medical and depression history, information on depression, associated symptoms, concomitant pathologies, and treatments. GPs assessed patients' depression status with the HRSD. The original version contains 17 items. The total score is interpreted as normal (0–7), mild (8–13), moderate (14–18), severe (19–22), and very severe depression (>23). Patients' clinical condition was assessed by the GP with the Clinical Global Impression – severity (CGI-S) scale evaluating the severity of psychopathology on D1–D7. The day after V1, patients completed an electronic notebook with information on their depression and completed the Hospital Anxiety and Depression Scale (HADS). The HADS, commonly used to determine levels of anxiety and depression, is a 14-item scale: seven items relate to anxiety and seven to depression. The HADS was also completed after 2, 4, and 6 weeks of supplementation. The Patient Global Impression of Change (PGIC) scale, a 9-point self-rated questionnaire assessing the change of patient clinical condition following a treatment, was completed by patients after 2, 4, and 6 weeks of supplementation. On the second visit after 6 weeks of supplementation (V2, D42), GPs performed a medical examination to reassess the situation. Adverse events and concomitant therapies were collected in the source medical record and on an electronic end-of-visit form. Patient depression status according to the HRSD was reassessed, as well as the CGI-S. CGI – improvement (CGI-I) was also used by the GP to evaluate the change from the initiation of treatment on a 7-point scale. Satisfaction and compliance were evaluated.

Evaluation criteria

The main end point was the evolution of HRSD score (components 1–17) after 6 weeks of supplementation. HADS, PGIC, CGI-S, and CGI-I scores, patient satisfaction, safety, and compliance were secondary-evaluation criteria.

Statistical analysis

According to results observed in several published studies with saffron and rhodiola extracts, a 4-point decrease in HRSD score after 6 weeks of supplementation was deemed relevant.[17,23,24,30] Given a 4-point decrease in HRSD score and considering a risk of error of α=5%, SD of 5 points, intrapatient correlation of 0.1, and power of 90%, the sample size was estimated to be at least 26 patients (paired *t*-test, one-sided).

Continuous variables are presented as mean ± SD. Categorical variables are presented as percentages. Paired Student's *t*-tests or Wilcoxon signed-rank tests were used depending on the normality or abnormality of data distribution for the comparison of HRSD, HADS, and CGI scores. A Spearman correlation test was performed to analyze the correlation between the evolution of HRSD score and its value at baseline. Analyses were performed on intention-to-treat (ITT), modified ITT (mITT; patients who took at least one dose of supplementation and who had a V2), and per protocol (PP) populations. Safety analysis was performed on all patients who had received at least one dose of treatment. All statistical analyses were performed with SAS software version 9.4. In all tests, $P<0.05$ was considered statistically significant.

Results

A total of 59 patients were screened and enrolled by 16 GPs between November 2016 and March 2017. Five patients were lost to follow-up (including the loss of two patients due to discontinuation of one GP) and nine were excluded for not meeting inclusion criteria (Figure 1). Therefore, 45 patients who had received at least one dose of supplement were included in the safety population. During the supplementation period, four patients dropped out (three mistakenly included and one lost to follow-up). In the end, 41 patients completed the study and were included in the mITT population. Four were excluded from the PP population because of poor compliance or intake of concomitant medications that were not authorized. As such, 37 patients were included in the PP population.

Patient characteristics

Patients were mainly women (82.2%, 37 of 45 patients, safety population; Table 1), among which 43.2% were menopausal (16 of 37). Mean age at inclusion was 47.6±14.6 years. A total of 28 of 45 patients (63.6%) had declared in their electronic notebooks suffering from depression at least once in their life; five of 28 (17.9%) had taken antidepressants. The first depressive episode had occurred 13±12 years (156.2±144.7 months) before inclusion (median 10.5 [0.5–50.0] years). Seven of 45 patients (15.6%) had family members who had a history of depression, more frequently the mother (four of seven, 57.1%). The average duration of the ongoing depressive episode was 4.4±4.5 (median 3 [1–24]) months.

Eighteen of 45 patients (40%) had had surgery or a medical history other than depression. Fourteen of 45 patients (31.1%) continued their ongoing treatment (other than for depression) during supplementation, with a total of 28 treatments declared. The drugs were taken more frequently for

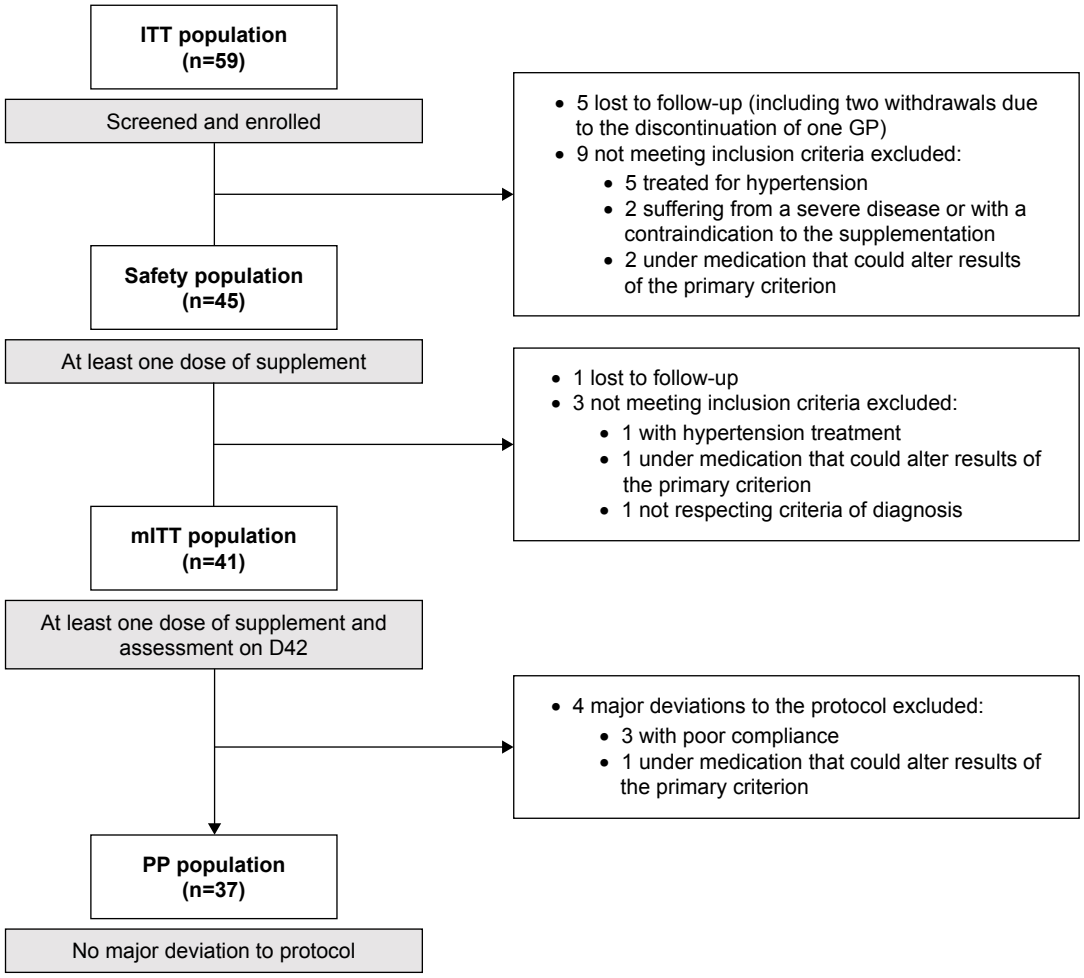

Figure 1 Flow diagram.
Abbreviations: GP, general practitioner; mITT, modified intention-to-treat; D42, day 42; PP, per protocol.

obstructive airway diseases (20%, nine of 45), cardiovascular diseases (15.6%, seven of 45), and nervous-system disorders (11.1%, five of 45).

HRSD scores

A significant decrease in HRSD scores of 58%±28.5% was observed after 6 weeks of supplementation: from 13.6±2.3 at D0 to 5.6±3.8 at D42 (7.9±4.2, 95% CI 9.29–6.61; $P<0.0001$, n=41). At D42, HRSD score had reduced by at least 20% in 87.8% of patients (36 of 41, 95% CI 74.00%–95.14%). According to HRSD-score classes, 53.7% (22 of 41) of patients had mild depression and 46.3% (19 of 41) moderate depression at D0. After 6 weeks of supplementation, HRSD score had decreased by 53.7%±29.6% (6.3±3.6 points) in mildly depressive patients (n=22), whereas it had decreased by 62.9%±27% (9.8±4.3 points) in patients suffering from moderate depression (n=19). The Spearman correlation coefficient between HRSD-score evolution and HRSD score at inclusion was –0.5, indicating significant opposing variation trends between the two variables: score decreases were greatest in patients with the highest scores at D0.

At D42, depressive symptoms had improved in 85.4% of patients (35 of 41), were stable in 12.2% (five of 41), and worse in one patient (2.4%). Patient distribution into the HRSD classes was significantly different from that observed at D0 ($P<0.0001$, Figure 2), with 29 patients (70.7%, 29 of 41)

Table 1 Patient characteristics

	Safety population (n=45)	PP population (n=37)
Women	37 (82.2%)	30 (81.1%)
Men	8 (17.8%)	7 (18.9%)
Age (years)	47.6±14.6	47.0±14.2
Patient history of depression	20 (44.4%)	16 (43.2%)
Family history of depression	7 (15.6%)	7 (18.9%)
Duration of ongoing depressive episode (months)	4.4±4.5	4.0±3.6
Surgery or medical history[a]	18 (40.0%)	15 (40.5%)

Note: [a]Patients who declared having suffered or suffering from at least one disease other than depression.
Abbreviation: PP, per protocol.

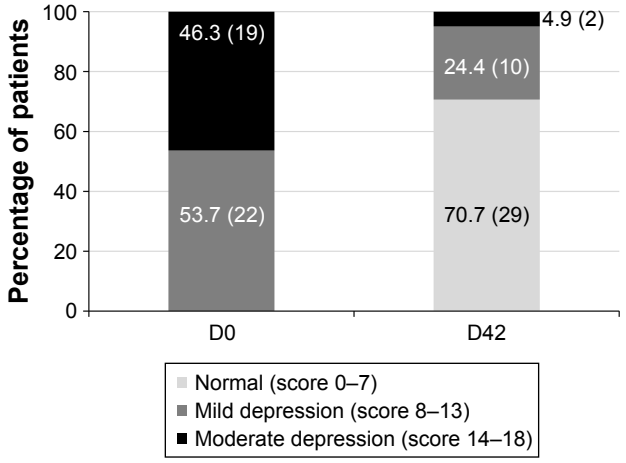

Figure 2 Patients' distribution into HRSD classes at day 0 (D0) and D42 (% [n], modified intention-to-treat population).
Abbreviation: HRSD, Hamilton Rating Scale for Depression.

no longer suffering from depression at D42. In addition, only two of 41 patients (4.9%) were suffering from moderate depression at D42 compared to 19 of 41 (46.3%) at D0.

HADS scores

A significant drop in both the HADS anxiety and depression scores was observed between D0 and D42. The decrease was 31.3%±23.2% for HADS anxiety: from 12.0±3.1 at D0 to 8.0±3.2 at D42 (3.9±3.3, 95% CI 2.86–4.99; $P<0.0001$), with a decrease of 46.1%±48.2% for HADS depression from 10.0±3.6 at D0 to 5.5±4.8 at D42 (4.4±5.5, 95% CI 3.09–6.40; $P<0.0001$). The drop was significant after 2 weeks of supplementation and throughout follow-up (Figure 3).

HADS anxiety scores decreased by at least 20% in 71.8% of patients (28 of 39, 95% CI 56.10%–83.58%) and HADS depression scores decreased by at least 20% in 66.7% (26 of 39, 95% CI 50.90%–79.44%). After 6 weeks of supplementation, patient distribution into the HADS classes was significantly different from that observed at D0 for the two scores ($P<0.0001$ for HADS anxiety and $P=0.0005$ for HADS depression, Figure 4). Globally, there was a progressive decline in prevalence of anxiety and depressive symptoms throughout the study.

CGI and PGIC scores

According to GPs' answers to CGI-S, only 14.6% (6 of 41) of patients were moderately or markedly depressive after 6 weeks of supplementation compared to 75.6% (31 of 41) before supplementation (Wilcoxon test $P<0.0001$, Table 2). GPs deemed that depression was very much improved in 78.1% (32 of 41) of patients after supplementation (CGI-I). In the PGIC, 56.4% (22 of 41) of patients declared feeling better after 2 weeks of supplementation, 62.5% (25 of 41) after 4 weeks, and 74.4% (29 of 41) after 6 weeks. All significant results in the mITT population were also significant in the PP population.

Compliance and safety

In the mITT population, information on compliance was available for 39 patients of 41. Thirty (76.9%) declared taking the supplementation without interruption and nine (23.1%) with a few missed days. Six patients of 45 in the safety population experimented at least one adverse event. Nine adverse events were listed: one dizziness, one vision blurred, one arthralgia, one lower-abdomen pain, one dry mouth, one fatigue, one nausea, and two upper-abdomen pain. These adverse events were of mild severity, completely recovered before the end of supplementation, and did not lead to discontinuation of supplementation. No serious adverse events were reported.

Discussion

In this preliminary study performed with recognized and validated criteria and measurement scales for the diagnosis

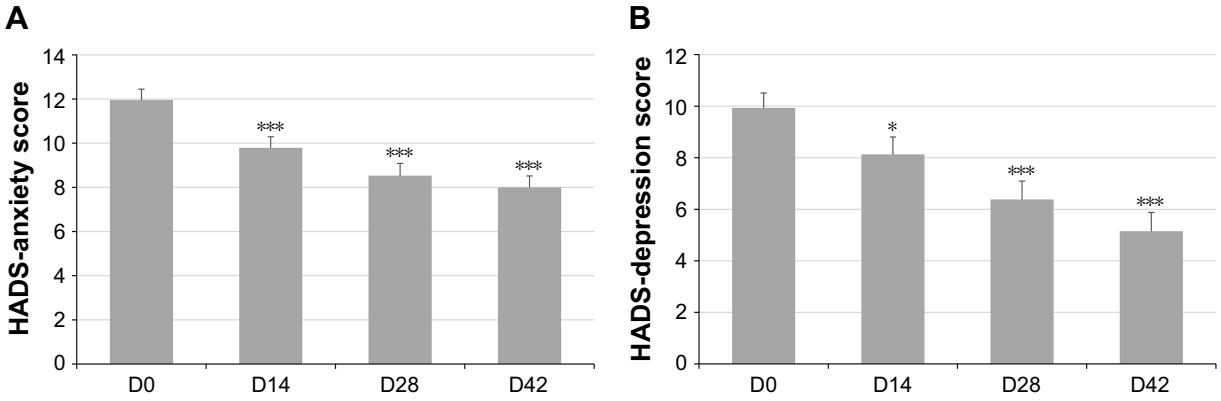

Figure 3 Evolution of HADS anxiety (**A**) and HADS depression (**B**) scores between day 0 (D0; n=40, mITT population) and D42 (n=39).
Notes: Data shown as mean ± SEM. *$P<0.05$, ***$P<0.0001$ versus D0.
Abbreviations: HADS, Hospital Anxiety and Depression Scale; mITT, modified intention-to-treat.

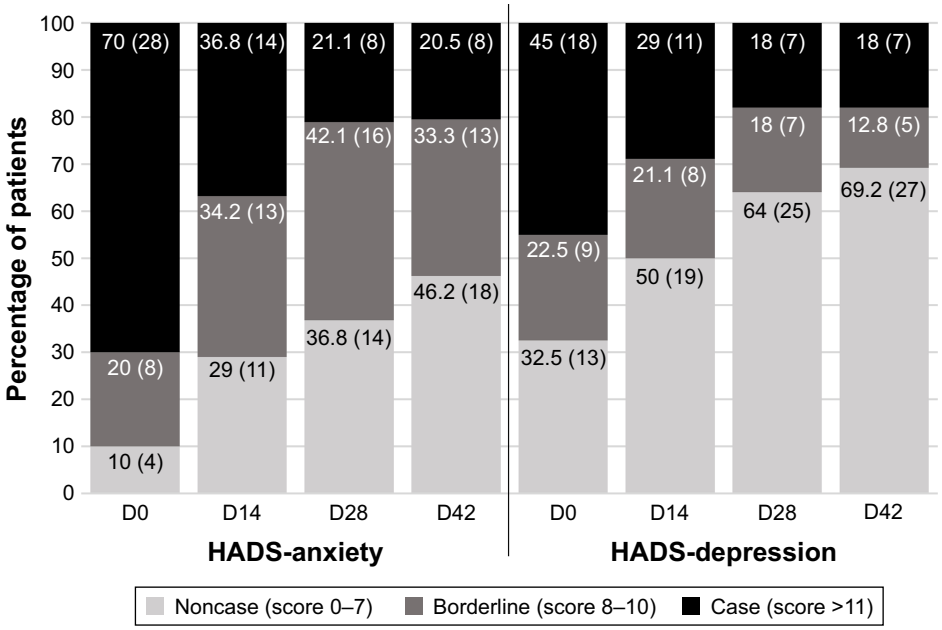

Figure 4 Evolution of patients' distribution into HADS classes between day 0 (D0) and D42 (% [n]; modified intention-to-treat population).
Abbreviation: HADS, Hospital Anxiety and Depression Scale.

and assessment of depression and anxiety, 6-week supplementation with a combination of rhodiola and saffron extracts was associated with a significant decrease in severity of depression in patients diagnosed as mildly to moderately ill at inclusion. Mean HRSD scores decreased by ~58% (~8 points) between the first and last visit 6 weeks later. To our knowledge, this is the first time that such a combination of rhodiola and saffron has been tested. Previously, rhodiola and saffron extracts were shown to have beneficial effects in patients suffering from MDD, but separately.[17,18,21–24,26,30]

The efficacy of saffron for the treatment of mild–moderate depression has been shown in several randomized double-blind clinical trials. In these studies, an extract of *C. sativus* stigmas at a dose of 30 mg per day for 6 weeks[24] and 100 mg per day for 12 weeks[21] was more effective than placebo. This extract (30 mg/day for 6 weeks) had similar effects to those of fluoxetine (20 mg/day)[17] and imipramine (100 mg/day).[23] Comparable effects were reported with a petal extract of saffron at 30 mg per day for 6 weeks vs placebo[18] and for 8 weeks vs fluoxetine (20 mg/day).[19]

Table 2 CGI and PGIC scores in the mITT population

CGI-S	D0	D42	CGI-I	D42
Normal, not at all ill	2.4% (1/41)	51.2% (21/41)	Very much improved	56.1% (23/41)
Borderline	4.9% (2/41)	21.9% (9/41)	Much improved	21.9% (9/41)
Mildly ill	17.1% (7/41)	12.2% (5/41)	Slightly improved	12.2% (5/41)
Moderately ill	39.0% (16/41)	12.2% (5/41)	No change	7.3% (3/41)
Markedly ill	36.6% (15/41)	2.4% (1/41)	Minimally worse	2.4% (1/41)
PGIC		**D14**	**D28**	**D42**
Worsening		2.6% (1/39)	0	0
No change		2.6% (1/39)	12.5% (5/40)	7.7% (3/39)
Almost the same, hardly any change		12.8% (5/39)	7.5% (3/40)	10.3% (4/39)
A little bit better, but no noticeable change		20.5% (8/39)	10% (4/40)	5.1% (2/39)
Somewhat better, but change does not make any real difference		5.1% (2/39)	7.5% (3/40)	2.6% (1/39)
Better, moderate change, but noticeable		41% (16/39)	12.5% (5/40)	20.5% (8/39)
Better, with a definite improvement that makes the difference		12.8% (5/39)	35% (14/40)	15.4% (6/39)
A great deal better, and a considerable improvement that makes all the difference		2.6% (1/39)	12.5% (5/40)	33.3% (13/39)
Complete recovery		0	2.5% (1/40)	5.1% (2/39)

Abbreviations: CGI-S, Clinical Global Impression – severity; PGIC, Patient Global Impression of Change; mITT, modified intention to treat.

In a randomized double-blind placebo-controlled clinical trial performed in 89 adults with mild–moderate DSM-IV MDD, Beck Depression Inventory and HRSD scores significantly declined in patients having received 340 or 680 mg of *R. rosea* rhizome extract (SHR5) per day over a 6-week period in comparison with patients having received the placebo, for whom scores were unchanged.[30] Overall depression, along with insomnia, emotional instability, somatization (at both doses), and self-esteem (only at the highest dose) were significantly improved after supplementation with *R. rosea*. In another randomized double-blind clinical trial in mild–moderate depression (57 patients randomized), supplementation with the same extract of *R. rosea*, also administered at 340 mg per day, but this time for 12 weeks, was compared to sertraline (50 mg/day) and placebo.[34] There was no significant difference between groups in changes in HRSD, Beck Depression Inventory, or CGI scores over time.

R. rosea is more known for its adaptogenic properties than antidepressant effects, and has proven benefits in patients with stress-related fatigue and anxiety.[35–37] An anxiolytic effect has also been reported for saffron.[22,38] In our study, after 6 weeks of supplementation with a combination of rhodiola and saffron, HADS anxiety scores were reduced significantly by >30%. This anxiolytic effect is particularly interesting, because the concurrent presence of a depressive disorder with prominent anxiety symptoms or an anxiety disorder is common in clinical practice.[39–41] It was estimated that >70% of individuals with depressive disorders also have anxiety symptoms and 40%–70% simultaneously met criteria for at least one type of anxiety disorder.[39,41] Previous studies have shown that patients with MDD with high levels of anxiety have a slower response to treatment,[42] and in some[41,43–46] but not all studies[47,48] were less likely to respond to antidepressants than patients with low levels of anxiety. In depressive patients treated with common antidepressants, such as citalopram and sertraline, more severe anxiety symptoms before treatment were associated with lower remission rates across all medications.[46] In some guidelines, it is considered that effective treatment of anxiety disorders will improve depression.[12]

In addition to the evaluation of depression and anxiety symptoms, both GPs and the patients were given the opportunity to rate their impression of the supplementation and its effects using the CGI and PGIC scales. The CGI allows clinicians to assess clinically relevant global response to treatment.[49] It has become one of the most widely used assessment tools in psychiatry, especially as an efficacy measure in clinical drug trials in different mental disorders,[50] as it makes results applicable for clinical practice. In our study, according to CGI-I scores, depression was much and very much improved in ~80% of patients, which was confirmed by the significant decrease in severity (CGI-S score). As an example, this scale has been used in a randomized double-blind placebo-controlled clinical trial in which 207 patients were treated with either a *Hypericum* extract or citalopram for a 6-week period. At the end of the study, according to the CGI-I, ~65% of patients treated with *Hypericum* and ~68% of patients treated with citalopram had their depression rated as much and very much improved.[51]

The PGIC is a clinical tool built to assess the patient's perceived impact of disease management. It allows patients to rate their overall status from the start of a study.[52] The scale is based on function and symptoms that are important for each individual patient. It provides a responsive and readily interpretable measure of participant assessment of the clinical importance of their improvement or worsening over the course of a study. In our study, nearly 75% of patients declared feeling better after supplementation, suggesting a beneficial impact of the combination of rhodiola and saffron on patients' perception of their disorder.

The main limitation of our study is obviously the absence of a control group. This study was observational; therefore, the effect of the combination tested might have been overestimated. The combination tested was well tolerated, with nine adverse events reported by six patients. These adverse events were of mild severity and did not lead to discontinuation of supplementation. Minor side effects have been associated with rhodiola, including dizziness and dry mouth.[53] A root extract of rhodiola was previously reported to be associated with fewer adverse events and better tolerated than a conventional antidepressant in patients with depression.[34] No adverse events were observed in Darbinyan et al.[30] In placebo- and antidepressant-controlled clinical trials, saffron was mainly associated with nausea, decreased appetite, anxiety, and headache, but those side effects were also observed with placebo and much less numerous than with antidepressants.[22,54]

Conclusion

Altogether, the results of this preliminary study performed in primary care suggest that the tested supplement containing rhodiola and saffron extracts could be of interest for the management of mild–moderate depression. There was a rapid improvement in both depressive and anxiety symptoms as assessed with the HRSD and the HADS, the CGI was much improved, and according to the PGIC a majority of patients felt better after supplementation. In addition, the combination of rhodiola and saffron was well tolerated. Benefits of the

combination will have to be confirmed in a double-blind placebo-controlled study.

Disclosure

MB, SAA, AB, CB, AG, and MD are employees of Groupe PiLeJe. PL is a consultant for PiLeJe. The authors report no other conflicts of interest in this work.

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