Original Paper

Efficacy of a standardised saffron extract (affron®) as an add-on to antidepressant medication for the treatment of persistent depressive symptoms in adults: A randomised, double-blind, placebo-controlled study

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Adrian L Lopresti[1,2], Stephen J Smith[1,2], Sean D Hood[3] and Peter D Drummond[1]

Abstract

Background: As a stand-alone intervention, saffron has efficacy for the treatment of mild-to-moderate depression. However, research as an adjunct agent is limited.

Aims: The effects of saffron as an adjunct to pharmaceutical antidepressants in adults with persistent depression was investigated.

Methods: In this eight-week, randomised, double-blind, placebo-controlled study, adults with persistent depression, currently taking a pharmaceutical antidepressant were given a placebo or a saffron extract (affron®, 14 mg b.i.d.). Primary outcome measures included the clinician-rated Montgomery–Åsberg Depression Rating Scale (MADRS) and self-rated MADRS (MADRS-S). Secondary outcome measures included the Antidepressant Side-Effect Checklist (ASEC) and Short Form-36 Health Survey (SF-36).

Results: Of the 160 participants enrolled, 139 provided usable data. Based on the MADRS, depressive symptoms decreased more in participants taking saffron compared with a placebo, with reductions of 41 and 21%, respectively ($p = 0.001$). However, scores on the MADRS-S decreased 27 and 26% in the saffron and placebo conditions, respectively ($p = 0.831$). Saffron was associated with a greater reduction in adverse effects of antidepressants ($p = 0.019$), although this was non-significant after covarying for baseline values ($p = 0.449$). Quality of life improved in both groups with no significant between-group differences ($p = 0.638$).

Conclusion: Adjunctive administration of a standardised saffron extract (affron®) for eight weeks was associated with a greater improvement in depressive symptoms as measured by the clinician-rated MADRS but not the self-report MADRS-S. Given the conflicting results, further research is needed to clarify the clinical benefits of saffron as an adjunctive treatment for adults with persistent depressive symptoms despite antidepressant drug treatment.

Keywords
Depression, saffron, adjunct treatment, herbal, antidepressant

Introduction

Pharmaceutical antidepressants such as selective-serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs) are the mainstay pharmacological treatments for adults with major depressive disorders. While these interventions have proven efficacy, a significant proportion of individuals obtain moderate-to-no benefit, as indicated by response and remission rates of approximately 60% and 30%, respectively (Cipriani et al., 2018; Papakostas et al., 2007; Rush et al., 2006). To enhance treatment efficacy, pharmacological options for clinicians include escalating the dose, substituting with an alternative antidepressant, or adjunct administration with another psychotropic medication. While this may be associated with improved treatment efficacy over time, there continues to remain a significant proportion of symptomatic patients (Adli et al., 2005; Jakubovski et al., 2016). In the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial, despite patients with major depressive disorder receiving up to four successive treatment modifications, 33% of patients continued to be symptomatic (Rush et al., 2006). Problems associated with dose escalation and adjunct medications include an increasing risk of adverse effects. This is a significant issue as adverse effects are a commonly-cited reason for treatment discontinuation (Burra et al., 2007; Sansone and Sansone, 2012).

Saffron, a spice derived from the stigmas of the *Crocus sativus* flower, has been investigated as a natural antidepressant in adults with mild-to-moderate depression in over 20 randomised

[1]College of Science, Health, Engineering and Education, Murdoch University, Perth, WA, Australia
[2]Clinical Research Australia, Perth, WA, Australia
[3]Division of Psychiatry, UWA Medical School, University of Western Australia, Perth, WA, Australia

Corresponding author:
Adrian L Lopresti, College of Science, Health, Engineering and Education, Murdoch University, 38 Arnisdale Road, Perth, WA 6023, Australia.
Email: a.lopresti@murdoch.edu.au

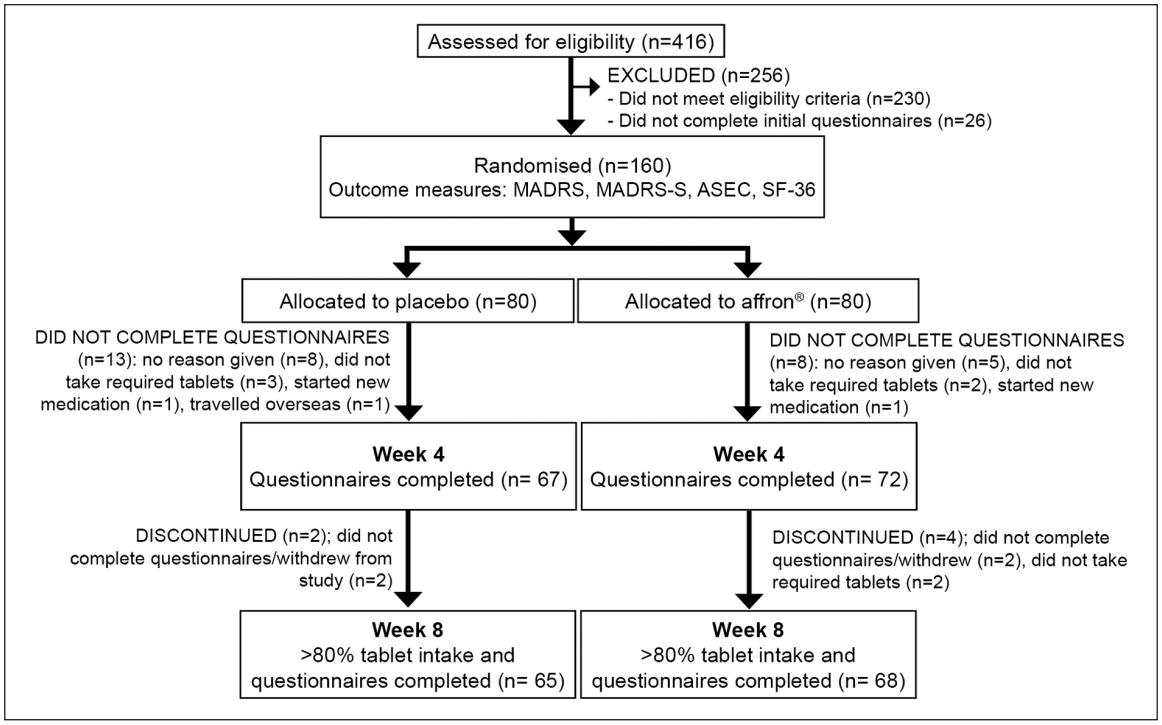

Figure 1. Systematic illustration of study design.

trials. The results from several meta-analyses have confirmed that it has greater efficacy compared with a placebo, with large effect sizes (Hausenblas et al., 2013; Lopresti and Drummond, 2014; Marx et al., 2019; Toth et al., 2018). In head-to-head comparisons with the pharmaceutical antidepressants fluoxetine, citalopram and imipramine, comparable efficacy has also been identified (Akhondzadeh et al., 2004; Akhondzadeh Basti et al., 2008; Ghajar et al., 2017). Given these positive findings, saffron presents as a possible adjunct to pharmaceutical antidepressants to increase treatment outcomes and possibly lower adverse side effects. There is previous research to suggest that saffron may be a beneficial adjunct option; however, results have been inconsistent and the strength of these findings is compromised by the small sample sizes ($n = 40$) and short treatment duration of four weeks (Jelodar et al., 2018; Sahraian et al., 2016; Talaei et al., 2015).

The goal of this study was to investigate the adjunct antidepressant effects of a standardised saffron extract (affron®) in adults with persistent depression, currently taking a pharmaceutical antidepressant. This study extends on previous research as a larger sample size was recruited and the effects of saffron over a longer treatment duration of eight weeks was examined. In addition, the effects of saffron on adverse effects and quality of life were investigated.

Materials and methods

Study design

This was a parallel, eight-week, randomised, double-blind, placebo-controlled trial (Figure 1). The trial protocol was approved by the Human Research Ethics Committee at Murdoch University, Western Australia, and was prospectively registered with the Australian New Zealand Clinical Trials Registry (Trial ID. ACTRN12618000748213). Participants were recruited across Australia through social media advertisements between July and November 2018.

Participants were randomly and equally assigned to two groups (placebo or affron®) using a randomisation calculator (http://www.randomization.com). The randomisation structure comprised 16 randomly permuted blocks, containing 10 participants per block. Participant identification number was allocated according to the order of participant enrolment in the study. All tablets were packed in identical bottles labelled by two intervention codes. These codes were held by the sponsor and a university investigator not directly involved in study recruitment and data collection. Participants and study investigators were not informed of treatment group allocation until all questionnaires were completed.

An a priori power analysis was undertaken to estimate the required sample size (based on a single outcome variable). In a recent meta-analysis on the antidepressant efficacy of saffron an effect size of 0.99 (combined across clinician-ratings and self-report) was identified in placebo-controlled studies (Marx et al., 2019). As this was an add-on study that included both clinician-ratings and self-report as primary outcome variables, sample size calculations were based on a more conservative effect size of 0.5. Assuming a power of 80% and a type one error rate (alpha) of 5%, the number of participants required per group to find an effect for the MADRS was estimated as 64. After allowing for a 20% drop out rate, we aimed to recruit 80 participants per group (Soper, 2019).

Participants

Inclusion criteria. Physically healthy, male and female participants aged 18–65 years, currently taking a stable dose (at least eight weeks) of a single pharmaceutical antidepressant, were included in the study. Despite antidepressant treatment, participants continued to suffer from mild-to-moderate depressive symptoms as assessed by a score greater than six on the Montgomery–Åsberg Depression Rating Scale (MADRS) (nine-items). Participation in psychological therapy was permissible if treatment commenced at least eight weeks prior to the study and there was no plan to modify or commence a new psychological treatment during participation in the study. Participants were also required to be fluent in English and to have consented (via a written consent form) to all pertinent aspects of the trial.

Exclusion criteria. Participants with a current or 12-month history of any psychiatric disorder other than mild-to-moderate depression or anxiety were ineligible to participate in the study. Participants who were engaging in self-harm behaviours and/or reported serious suicidal ideation were also excluded from the study. Participants currently taking any pharmaceutical medication, apart from a single pharmaceutical antidepressant, oral contraceptives and the occasional use (no more than fortnightly) of analgesics (e.g. ibuprofen, paracetamol), or who were currently taking saffron supplements and/or other herbal supplements were also excluded from the study. A current or history of a clinically significant, chronic medical condition including cardiovascular disease, organic brain disorder, seizure, diabetes, severe obesity, or use of illicit drugs also resulted in exclusion from study participation. Pregnant women, women who were breastfeeding, or women intending to fall pregnant were also ineligible to participate in the study. Participants were also ineligible if they reported a greater than ten-year continuous use of antidepressant medication with no remission in depressive symptoms greater than six months over this period. Participants were informed that modification in antidepressant dose or type, or participation in a new psychological therapy during the study would result in exclusion.

Eligibility was initially assessed via the completion of an online questionnaire that screened for current medication use, suicidal ideation, self-harm behaviours, history of medical/ psychiatric disorders, alcohol, nicotine and other drug use, supplement and vitamin intake, and pregnancy/breastfeeding status. If assessed as likely eligible, volunteers participated in a phone interview with an investigator. The phone interview comprised a structured series of questions examining the eligibility criteria specified above.

Interventions

Placebo and active tablets were identical in appearance, being matched for colour coating, shape and size. The active treatment, supplied by Pharmactive Biotech Products SL, contained 14 mg of a standardised saffron extract (affron®), derived from the stigmas of *Crocus sativus L.* and standardised to contain $>$ 3.5% Lepticrosalides®, a measure of bioactive compounds present in saffron, including safranal and crocin isomers.

The saffron stigmas were cultivated in Alborea (Albacete, Spain) and extracted in the factory of Pharmactive Biotech Products SL in Madrid (Spain) to produce affron® 3.5% Lepticrosalides®. The placebo tablets contained the same excipients as the active tablet (microcrystalline cellulose and calcium hydrogen phosphate). All tablets were manufactured and packed in an Australian Therapeutic Goods Administration registered plant.

All participants were instructed to take one tablet, twice daily, with or without food for eight weeks. Medication adherence was measured by tablet count by the participant at weeks 4 and 8. The participant's prescribing doctor was not involved in the study. Efficacy of participant treatment blinding was examined by asking participants to predict group allocation (placebo, saffron, or uncertain) at the completion of the study.

Saffron and placebo tablets were posted to participants with directions for use provided on tablet bottles. Participants were also provided with an information sheet about tablet intake and what to do if they missed a dose. This information was also verbally conveyed to participants during their initial telephone interview.

At the end of the trial, participants taking the placebo were offered a free eight-week supply of saffron. Participants interested in continuing to take saffron tablets were provided with information on where the tablets could be purchased.

Outcome measures

Primary outcome measures

Montgomery –Åsberg Depression Rating Scale (MADRS). The MADRS is a 10-item, clinician-rated questionnaire designed to measure the severity of depressive symptoms in adults. As ratings in this study were based on a phone interview, one question referring to the patient's physical presentation of apparent sadness was not rated. Therefore, only nine items were used as a measure of depression severity. The questions in the MADRS assess symptoms of sadness, tension, sleep, appetite, concentration, initiative, interest, pessimism and suicidal ideation. The MADRS is a commonly-used, reliable and valid depression measure regularly used as an outcome measure in antidepressant trials and is sensitive to treatment changes (Iannuzzo et al., 2006; Montgomery and Asberg, 1979; Quilty et al., 2013). To maintain assessment consistency, the assessing investigator used the structured interview guide for the Montgomery–Åsberg Depression Rating Scale (SIGMA) which has demonstrated high inter-rater reliability (Williams and Kobak, 2008). MADRS questions are rated on a seven-point scale ranging from 0 to 6, resulting in a maximum score of 54 (for the nine items rated in this study). Scores of 7 or greater reflect mild depressive symptoms.

Montgomery –Åsberg Depression Rating Scale, self-report (MADRS-S). The MADRS-S is a self-rated version of the original clinician-rated MADRS (Svanborg and Asberg, 1994). It comprises nine items assessing depressive symptoms as used in the clinician-rated version. The MADRS-S correlates moderately with the MADRS and is recommended as a complementary assessment instrument to the MADRS (Bondolfi et al., 2010; Fantino and Moore, 2009). MADRS-S questions are rated on a seven-point scale, ranging from 0 to 3 inclusive of half points, resulting in a maximum score of 27. To enable a direct comparison with the MADRS, scores were doubled, resulting in a maximum score of 54.

Secondary outcome measures

Short Form-36 Health Survey (SF-36). The SF-36 is a self-report measure assessing quality of life. It consists of eight scaled scores measuring (a) vitality, (b) physical functioning, (c) bodily pain, (d) general health perceptions, (e) physical role functioning, (f) emotional role functioning, (g) social role functioning, and (h) mental health. The SF-36 is a commonly-used outcome measure of quality of life with strong psychometric properties (McHorney et al., 1993; Ware and Sherbourne, 1992). Scoring for the SF-36 was based on the algorithm developed by RAND Health Care (Hays et al., 1993).

Antidepressant Side-Effect Checklist (ASEC). The ASEC is a self-report instrument measuring 21 adverse reactions to antidepressants: dry mouth, drowsiness, difficulty sleeping (insomnia), blurred vision, headache, constipation, diarrhoea, increased appetite, decreased appetite, nausea or vomiting, problems with urination, problems with sexual function, palpitations, feeling light-headed on standing (orthostatic dizziness), feeling like the room is spinning round (vertigo), sweating, increased body temperature, tremor, disorientation, yawning and weight gain. The ASEC has good agreement between self-report and psychiatrists' ratings of adverse effects (Uher et al., 2009) and has been used to assess adverse effects in antidepressant trials (Berm et al., 2015; Bet et al., 2013).

Satisfaction ratings. To examine satisfaction and tolerability associated with tablet intake, participants rated (on a five-point Likert scale) the following two questions: (a) How satisfied were you with the intake of your tablets? (b) If you were taking saffron, how likely is it that you would continue to take it?

Outcomes measures were completed at baseline, week 4 and week 8 with self-report measures completed online (MADRS-S, SF-36, and ASEC) and the MADRS administered by telephone. Satisfaction ratings were made at week 8 only through an online questionnaire.

Statistical analysis

An independent samples *t*-test was used to compare demographic variables across the two treatment groups for continuous variables, and Pearson's Chi-square was used to compare categorical data. Total scores on the MADRS, MADRS-S, and ASEC, and subscale scores on the SF-36 were analysed for time (baseline, week 4 and week 8) and treatment (saffron and placebo) effects using a mixed repeated-measures analysis of variance (ANOVA). An independent samples *t*-test was conducted to compare between-group percentage change in MADRS scores over time (week 0 to week 8) and a Cohen's D analysis was undertaken to examine effect sizes.

Based on the visual inspection of Q–Q plots there were no significant outliers with data fulfilling the criteria for normality. Standardised scores for the SF-36 were used. Where necessary, degrees of freedom were adjusted using the Greenhouse-Geisser approach to correct for violations of the sphericity assumption. Data from participants were included in analyses if questionnaire data were obtained at week 4 last observation carried forward (LOCF) from week 4 for missing values). A Bonferroni correction was applied to the criterion of statistical significance for analyses involving the two primary outcome measures (i.e. the criterion was $p < 0.025$ for these analyses). All data were analysed using SPSS (version 24; IBM, Armonk, NY).

As there were inconsistencies in outcomes as measured by the MADRS and MADRS-S, a post-hoc analysis was undertaken to examine the relationship between the measures. Pearson's *r* correlations between MADRS and MADRS-S total score and individual item ratings were conducted. An exploratory repeated-measures ANOVA was also undertaken on individual item measures in the MADRS to identify specific symptomatic areas of change.

Results

Study population

Baseline questionnaire and demographic information. From 416 people screened for participation in the study, 160 volunteers met eligibility criteria and were enrolled for study participation. Baseline demographic details are included in Table 1 and baseline outcome measures are detailed in Table 2. Data from 139 participants were used for statistical analyses and 133 participants completed all study requirements (i.e. consumed > 80% of tablets and completed all self-report inventories) over the eight-week trial. Fifteen participants dropped out or did not adhere to capsule intake in the placebo condition and 12 in the active-treatment condition. There were no significant differences between the dropout rates across groups. Reasons for withdrawal included failure to complete questionnaires and/or participate in phone interviews ($n = 17$), inconsistent tablet intake (n = 7), change in medication ($n = 2$), and sudden overseas travel ($n = 1$). No participants withdrew from the study due to reported adverse events associated with tablet intake.

Outcome measures

MADRS (primary outcome measure). Changes in MADRS scores across the two treatment groups and repeated measures ANOVA significance levels are detailed in Table 3 and Figure 2. A statistically significant time × group interaction was calculated on the MADRS scores ($F_{2,274} = 6.67$, $p = 0.001$). Time contrasts revealed a significant time × group interaction from week 4 to week 8 ($F_{1,137} = 11.21$, $p = 0.001$) but not from week 0 to week 4 ($F_{1,137} = 1.93$, $p = 0.167$), with a significant reduction in MADRS score in the saffron group from week 4 to week 8 ($T(71) = 3.22$, $p = 0.002$). As demonstrated in Figure 3, there was a 41.28% reduction in MADRS scores from baseline to week 8 in the saffron group compared with a 20.59% reduction in the placebo group. An independent samples *t*-test confirmed that these differences were statistically significant ($T(137) = 3.431$, $p = 0.001$] with a Cohen's D effect size of 0.58.

Changes in MADRS-S scores across the two treatment groups and repeated measures ANOVA significance levels are detailed in Table 3 and Figure 2. There was no statistically significant time × group interaction on the MADRS-S scores ($F_{2,274} = 0.098$, $p = 0.907$). As demonstrated in Figure 3, there were similar reductions in MADRS-S scores from baseline to week 8 in the saffron (26.81% reduction) and the placebo group (26.00% reduction). An independent samples *t*-test confirmed non-significant differences in these scores ($T(137) = 0.213$, $p = 0.831$).

Table 1. Baseline demographic details of participants.

		Saffron	Placebo
Sample size (*n*)		80	80
Age (mean and SE)		40.4 (1.44)	39.65 (1.31)
BMI (mean and SE)		25.79 (0.53)	27.07 (0.51)
Gender (*n*)	Female	57	56
	Male	23	24
Marital status (*n*)	Single	36	26
	Married	30	37
	Defacto	14	17
Educational level (*n*)	Secondary	34	35
	Tertiary	30	24
	Post-graduate	16	21
Exercise frequency	Never/rarely	18	21
	1–2 times a week	12	12
	3–5 times a week	30	24
	6+ times a week	20	23
Length of time on antidepressant	less than 6 months	5	10
	6–12 months	17	18
	1–2 years	20	15
	2–5 years	20	17
	5–10 years	14	14
	10+ years	4	6
Depression severity	Mild	26	29
	Moderate	51	51
	Severe	3	0
Antidepressant class (*n*)	SSRI	44	45
	SNRI	23	28
	Melatonergic agent	2	5
	TCA	6	1
	Other	5	1
Antidepressant type (*n*)	Escitalopram	19	20
	Citalopram	7	5
	Sertraline	11	7
	Fluoxetine	7	9
	Paroxetine	0	2
	Vortioxetine	0	2
	Desvenlafaxine	8	14
	Venlafaxine	8	8
	Duloxetine	7	6
	Amitriptyline	6	0
	Deptran	0	1
	Agomelatine	2	5
	Mirtazapine	4	1
	Moclobemide	1	0

SSRI: selective-serotonin reuptake inhibitor; SNRI: serotonin-noradrenaline reuptake inhibitors; TCA: tricyclic antidepressant.

A per protocol analysis comprising 133 participants who completed the treatment demonstrated consistent findings to the LOCF analysis. There was a statistically significant time × group interaction for the MADRS ($F_{2,262} = 6.96, p = 0.001$). However, no significant between-group differences were observed on MADRS-S scores ($F_{2,262} = 0.127, p = 0.881$).

An examination of response rates (defined as a 50% reduction in total score from baseline) was conducted across treatment conditions. Based on the MADRS, 40% of participants in the saffron group achieved a treatment response compared with 24% in the placebo group. However, for the MADRS-S, response rates were similar in the saffron and placebo groups (13 and 18% respectively). Remission rates could not be calculated as a remission cut-off score for the nine-item MADRS used in this study was not available.

Table 2. Baseline outcome measures of participants.

	Saffron (mean and SE)	Placebo (mean and SE)
MADRS	21.73 (0.78)	19.95 (0.79)
MADRS-S	21.93 (0.60)	21.63 (0.66)
ASEC	10.89 (0.68)	10.41 (.70)
SF-36 Physical Functioning	86.13 (1.69)	87.69 (1.61)
SF-36 Role Functioning	63.75 (4.00)	68.13 (4.05)
SF-36 Role Functioning Emotional	26.68 (3.78)	31.25 (4.00)
SF-36 Energy/Fatigue	27.13 (1.71)	25.21 (1.98)
SF-36 Emotional Wellbeing	44.90 (1.63)	47.28 (1.85)
SF-36 Emotional Functioning	52.58 (2.17)	52.73 (2.51)
SF-36 Pain	73.48 (2.23)	72.36 (2.43)
SF-36 General Health	55.44 (1.98)	56.25 (2.18)

MADRS: Montgomery–Åsberg Depression Rating Scale; MADRS-S: self-rated MADRS; ASEC: Antidepressant Side-Effect Checklist

ASEC (secondary outcome measure 1). Changes in ASEC scores across the two treatment groups and repeated measures ANOVA significance levels are detailed in Table 3 and Figure 4. A statistically significant time × group interaction was found on ASEC scores ($F_{1.9,260.3} = 4.213, p = 0.017$). Time contrasts revealed a significant time × group interaction from week four to week eight ($F_{1,137} = 5.63, p = 0.019$), but not week 0 to week 4 ($F_{1,137} = 2.14, p = 0.146$), with a significant reduction in ASEC score in the saffron group from week 4 to week 8 ($T(71) = 3.35$, $p = 0.001$). However, a univariate ANOVA with baseline ASEC entered as a covariate revealed between-group ASEC scores at week 8 did not differ significantly between the saffron and placebo conditions ($F_{1,136} = 0.557, p = 0.449$).

SF-36 (secondary outcome measure 2). Changes in SF-36 sub-scale scores across the two treatment groups and repeated measures ANOVA significance levels are detailed in Table 3. The multivariate test confirmed a non-significant time × group interaction ($F_{16,536} = 0.841, p = 0.638$). Univariate analyses also demonstrated non-significant time × group interactions for all SF-36 subscale scores.

Satisfaction ratings. In response to the question 'How satisfied are you with the intake of your tablets', a mean rating of 3.64 (SE = 0.10) (ratings from 1 to 5) was reported by participants in the saffron group, with 4% of respondents indicating they were a little dissatisfied with their tablet intake. A mean rating of 3.51 (SE = 0.10) was found in the placebo group with 2% indicating they were not at all satisfied and 8% a little dissatisfied. An independent samples *t*-test confirmed no statistically significant differences between the ratings across the two conditions ($T_{130} = 0.949, p = 0.344$).

Table 3. Changes in outcome measures over time.

			Week 0	Week 4	Week 8	*p*-value[a]	*ES*[b]
MADRS	Saffron ($n = 72$)	Mean	21.76	15.44	13.03	0.001	0.58
		SE	0.82	0.92	1		
	Placebo ($n = 67$)	Mean	20.03	15.28	15.43		
		SE	0.91	0.96	1.05		
MADRS-S	Saffron ($n = 72$)	Mean	22.25	16.82	16.04	0.907	0.04
		SE	0.63	0.66	0.63		
	Placebo ($n = 67$)	Mean	21.67	16.57	15.43		
		SE	0.74	0.69	0.65		
ASEC	Saffron ($n = 72$)	Mean	10.76	10.33	8.75	0.016	0.18
		SE	0.714	0.76	0.74		
	Placebo ($n = 67$)	Mean	9.66	8.07	8.58		
		SE	0.65	0.68	0.74		
SF-36 subscale scores							
Physical functioning	Saffron ($n = 72$)	Mean	86.11	85.42	87.5	0.980	0.01
		SE	1.803	1.886	1.752		
	Placebo ($n = 67$)	Mean	89.10	88.06	90.37		
		SE	1.52	1.79	1.51		
Role functioning	Saffron ($n = 72$)	Mean	63.19	70.83	75.69	0.391	0.21
		SE	4.28	4.17	3.99		
	Placebo ($n = 67$)	Mean	67.54	69.55	72.01		
		SE	4.51	4.76	4.34		
Role functioning emotional	Saffron ($n = 72$)	Mean	25.47	47.64	53.69	0.971	0.03
		SE	3.82	4.61	4.65		
	Placebo ($n = 67$)	Mean	31.85	54.19	58.81		
		SE	4.35	4.70	4.90		
Energy/fatigue	Saffron ($n = 72$)	Mean	27.01	36.81	40.76	0.424	0.10
		SE	1.85	2.14	2.36		
	Placebo ($n = 67$)	Mean	25.55	38.96	40.97		
		SE	2.20	2.55	2.56		
Emotional wellbeing	Saffron ($n = 72$)	Mean	45.39	55.39	56.39	0.115	0.15
		SE	1.70	2.05	1.98		
	Placebo ($n = 67$)	Mean	46.48	61.91	60.03		
		SE	2.12	1.91	2.11		
Emotional functioning	Saffron ($n = 72$)	Mean	51.61	65.78	65.06	0.890	0.03
		SE	2.26	2.38	2.39		
	Placebo ($n = 67$)	Mean	54.15	67.21	68.18		
		SE	2.65	2.72	2.70		
Pain	Saffron ($n = 72$)	Mean	74.13	71.57	77.03	0.633	0.07
		SE	2.38	2.79	2.01		
	Placebo ($n = 67$)	Mean	73.33	74.04	77.55		
		SE	2.63	2.96	2.44		
General health	Saffron ($n = 72$)	Mean	54.79	57.85	59.93	0.200	0.20
		SE	2.16	1.98	1.92		
	Placebo ($n = 67$)	Mean	56.42	63.13	64.25		
		SE	2.41	2.21	2.45		

[a]*p*-value repeated measures analysis of variance (ANOVA) time × group interaction; [b] Cohen's D effect size.
MADRS: Montgomery–Åsberg Depression Rating Scale; MADRS-S: self-rated MADRS; ASEC: Antidepressant Side-Effect Checklist

In response to the question, 'If you were taking saffron, how likely is it that you would continue to take it', a mean rating of 3.54 (SE = 0.13) (ratings from 1 to 5) was found in the saffron group with 14% of respondents indicating they were unlikely or very unlikely to continue to take it. A mean rating of 3.09 (SE = 0.16) was identified in the placebo group, with 32% of respondents reporting they were unlikely or very unlikely to continue to take it. An independent samples *t*-test confirmed a statistically significant higher rating in the saffron group compared with the placebo group ($T(130)=2.209$, $p = 0.029$).

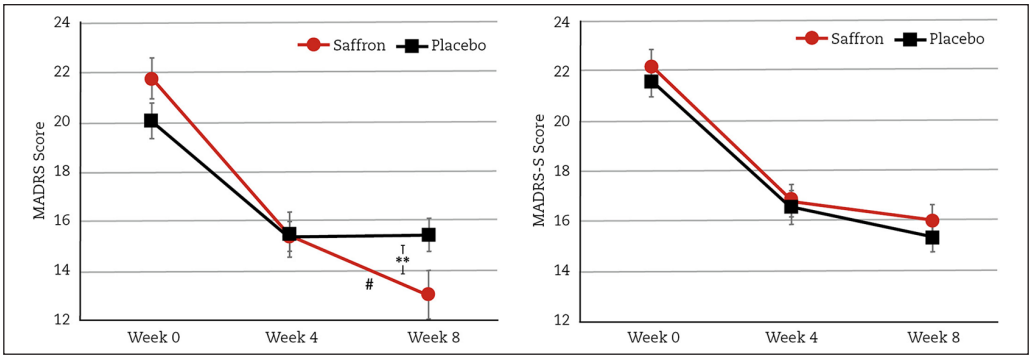

Figure 2. Change in Montgomery–Åsberg Depression Rating Scale (MADRS) and self-rated MADRS (MADRS-S) scores over time (error bars depict standard error).

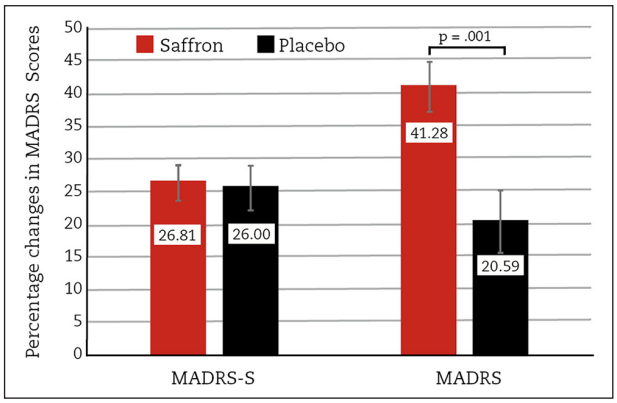

Figure 3. Percentage change in Montgomery–Åsberg Depression Rating Scale (MADRS) and self-rated MADRS (MADRS-S) over eight-week intervention (error bars depict standard error).

Post-hoc analyses

Relationship between MADRS and MADRS-S scores. Post-hoc analyses were undertaken to examine the association between the MADRS and MADRS-S ratings. As demonstrated in Table 4, time point correlations between corresponding questions on the MADRS and MADRS-S at week 0, week 4 and week 8 were statistically significant with correlations ranging from 0.302 (question examining interest in activities at week 8) to 0.669 (question assessing sleep quality at week 4). MADRS and MADR-S total scores were highly correlated at all time points ranging from 0.695 at baseline to 0.779 at week 4. However, correlations between change in MADRS and MADRS-S scores (baseline to week 8) were lower with ratings ranging from a non-statistically significant 0.100 for change in suicidal ideation ratings, to 0.418 for change in sleep quality. Change MADRS and MADRS-S total scores correlated moderately ($r = 0.512$).

A repeated measures ANOVA on individual questions on the MADRS-S demonstrated no statistically-significant time × group interaction on any MADRS-S items (Table 5). However, on the MADRS there were statistically-significant time × group interactions for questions assessing sleep quality, initiative/motivation, and interest/pleasure in activities.

Adverse events. No significant adverse events were reported by participants, with similar dropout rates across the two conditions. No participants withdrew from the study due to concerns associated with tablet intake. Further confirmation of safety and tolerability of tablet intake is provided by generally positive satisfaction ratings by participants in the study.

Efficacy of participant blinding. To evaluate the efficacy of condition concealment over the study, participants were asked at the completion of the study to predict condition allocation (i.e. placebo, saffron, or uncertain). Efficacy of group concealment was high as only 25% in the saffron group and 28% in the placebo group correctly guessed treatment allocation.

Discussion

In this eight-week, randomised, double-blind, placebo-controlled trial, the antidepressant efficacy of a standardised saffron extract (affron®) as an adjunct to pharmaceutical antidepressants in adults with persistent depression was demonstrated by the clinician-rated MADRS but not self-report version. Based on the more commonly-used, clinician-rated, MADRS, depressive symptoms decreased by 41% in participants taking saffron compared with 21% in those taking a placebo. An exploratory analysis revealed that based on the clinician-rated MADRS, symptomatic improvements from saffron occurred in sleep quality, initiative/motivation and interest/pleasure in activities, although further validation is required as these observations are based on ratings from single questions. In contrast to the positive findings from the clinician-rated MADRS, there were no differences between saffron and placebo based on the self-rated MADRS-S. There was a reduction of 27% in total score in participants allocated to the saffron condition compared with a 26% reduction in participants taking a placebo.

During weeks 4 to 8, adverse effects as assessed by the ASEC declined in participants taking saffron but plateaued in participants taking the placebo. However, this finding needs to be interpreted cautiously as discrepancies in baseline scores may account for differences in ASEC scores over time. The effects of saffron on specific adverse symptoms could not be adequately examined as ASEC scoring is based on severity ratings of 21 diverse symptoms. Moreover, it is unclear if these improvements are due to saffron's direct influence on antidepressant

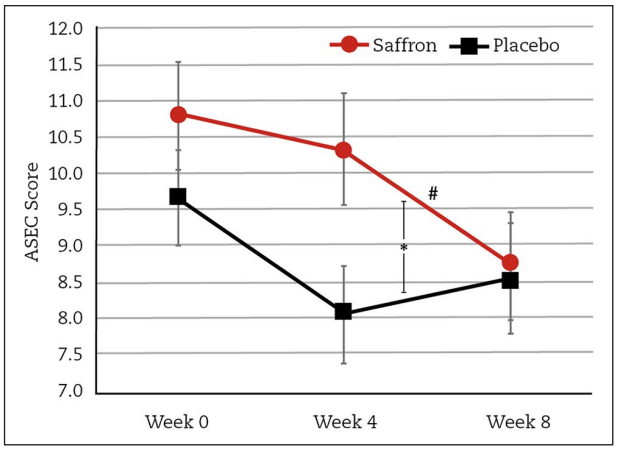

Figure 4. Changes in Antidepressant Side-Effect Checklist (ASEC) scores over time (error bars depict standard error).

Table 4. Correlations (Pearson's *r*) between Montgomery–Åsberg Depression Rating Scale (MADRS) and self-rated MADRS (MADRS-S) item and total scores.

n = 132	Week 0	Week 4	Week 8	Change from baseline
Sadness	0.506**	0.577**	0.547**	0.362**
Tension	0.421**	0.560**	0.591**	0.289**
Sleep	0.618**	0.669**	0.547**	0.418**
Appetite	0.630**	0.429**	0.459**	0.320**
Concentration	0.556**	0.457**	0.517**	0.402**
Initiative	0.518**	0.524**	0.503**	0.395**
Interest	0.441**	0.435**	0.302**	0.248*
Pessimism	0.567**	0.513**	0.626**	0.364**
Suicidal ideation	0.432**	0.557**	0.517**	0.100#
Total score	0.695**	0.779**	0.755**	0.512**

$^{**}p < 0.001$; * $p < 0.01$; # $p > 0.05$.

adverse effects or due to improvements in general mood. It is important to note that the ASEC is a self-report measure, and as previously mentioned, no differences in treatment efficacy between saffron and the placebo were identified based on the self-report MADRS-S. Therefore, the noted reductions in the ASEC are more consistent with the clinician-rated MADRS, where between-group differences in both measures occurred from weeks 4 to 8. It is speculated that saffron's anti-inflammatory and antioxidant effects may account for its positive influence on problematic symptoms although further research in this area is required (Boskabady and Farkhondeh, 2016; Boskabady et al., 2011; Poma et al., 2012; Razavi et al., 2013; Samarghandian et al., 2017).

In terms of changes in quality of life, there were no significant differences between saffron and placebo, where improvements occurred in both conditions. The SF-36 was used as a measure of quality of life where subscale scores for physical functioning, role functioning, energy/fatigue, emotional wellbeing/functioning, pain and general health are calculated. Improvements in most of these measures occurred over time, with no significant differences between saffron and the placebo.

Saffron was well-tolerated with no significant differences in self-reported adverse effects. No participant withdrew from the study due to self-reported adverse effects associated with their tablet intake. In fact, based on the ASEC, overall adverse effects decreased in the saffron group over time. Further confirmation of the tolerability associated with saffron intake is provided by the positive satisfaction ratings by participants at the end of the study. Only 4% of respondents taking saffron reported being dissatisfied with their tablet intake compared with 10% taking the placebo. When asked about the likelihood of them continuing to take the tablets (if it was saffron), 14% of participants taking saffron indicated they were unlikely to continue to take it, compared with 32% of respondents taking the placebo.

Despite these many positive findings, the non-concordant outcomes as measured by the clinician-rated and self-report versions of the MADRS remains a dilemma. An exploratory analysis comparing these two measures confirmed moderate-to-high time-point correlations in their total scores at weeks 0, 4 and 8 (correlations ranged from 0.70 to 0.78). These time-point correlations are within acceptable limits as findings from previous studies have demonstrated time-point correlations ranging from to 0.47 to 0.91 (Bondolfi et al., 2010; Cunningham et al., 2011; Fantino and Moore, 2009). Our time-point correlations are also consistent with those observed by Uher et al. (2012) and Reilly et al. (2015) who compared correlations using the clinician and self-rated versions of the Quick Inventory of Depressive Symptomatology. Concordance in delta changes in total scores between these two measures were lower (correlation of 0.512) but again were within levels consistent with the literature (Cunningham et al., 2011). Concordance in time-point and delta ratings on specific symptoms assessed by the MADRS scales were variable. In particular, agreement between changes in suicidal ideation, tension, and interest over the 8-week intervention was low. Fantino and Moore (2009) also demonstrated low correlations between suicide ratings when the two MADRS versions were administered to a depressed population participating in an antidepressant clinical trial. However, a high concordance in suicide ratings, but not initiative ratings, was identified by Bondolfi et al. (2010) when the measures were used in clinical practice. Several possibilities may account for the discrepant outcomes for the MADRS and MADRS-S. It has been confirmed in several meta-analyses on antidepressant trials, effect sizes from clinician-rated instruments are higher compared with self-rated instruments (Cuijpers et al., 2010; Greenberg et al., 1992). This suggests that clinician-rated instruments are more sensitive to antidepressant treatments than self-reports. Whether this is due to more accurate identification from clinician-rated instruments or an overestimation of therapeutic effects remains to be determined. Clinician-rated instruments have traditionally been considered gold-standard outcome measures in clinical trials but are hindered by the extra resources associated with their administration. Self-report measures are attractive options as they are less time-intensive than clinician-rated instruments. However, the evidence suggests that while the correlations between self-report and clinician-rated instruments are sound, they should be considered complementary outcome measures rather than stand-alone measures (Cuijpers et al., 2010; Dunlop et al., 2010). It is important to note that the MADRS is usually conducted face-to-face, although in the current study, assessments were conducted over the phone which may potentially account for the non-concordant findings. However, administering the MADRS by telephone has demonstrated strong concordance with face-to-face assessments, with two studies confirming no significant differences

Table 5. Change in Montgomery–Åsberg Depression Rating Scale (MADRS) and self-rated MADRS (MADRS-S) item and total scores over time.

Question	Group		MADRS-S					MADRS				
			Week 0	Week 4	Week 8	*p*-value[a]	ES[b]	Week 0	Week 4	Week 8	*p*-value[a]	ES[b]
Sadness	Saffron (n = 68)	Mean (SE)	2.15 (0.09)	1.54 (0.09)	1.59 (0.10)	0.142	0.05	3.01 (0.18)	1.57 (0.19)	1.59 (0.20)	0.182	0.28
	Placebo (n = 64)	Mean (SE)	2.03 (0.11)	1.67 (0.12)	1.42 (0.08)			2.77 (0.170	1.77 (0.20)	1.84 (0.21)		
Tension	Saffron (n = 68)	Mean (SE)	2.71 (0.11)	2.07 (.10)	2.16 (0.10)	0.254	0.11	2.60 (0.22)	2.07 (0.19)	1.75 (0.21)	0.555	0.19
	Placebo (n = 64)	Mean (SE)	2.69 (0.12)	2.23 (0.11)	2.03 (0.11)			2.25 (0.23)	1.88 (0.20)	1.73 (0.22)		
Sleep	Saffron (n = 68)	Mean (SE)	2.71 (0.15)	2.04 (0.14)	2.00 (0.14)	0.640	0.13	2.91 (0.22)	2.32 (0.20)	1.79 (0.18)	0.021	0.43
	Placebo (n = 64)	Mean (SE)	2.41 (0.15)	1.92 (0.13)	1.86 (0.13)			2.55 (0.21)	2.17 (0.22)	2.25 (0.21)		
Appetite	Saffron (n = 68)	Mean (SE)	1.44 (0.10)	1.25 (0.09)	1.15 (0.06)	0.157	0.13	0.76 (0.16)	0.59 (0.16)	0.51 (0.12)	0.584	0.16
	Placebo (n = 64)	Mean (SE)	1.61 (0.13)	1.13 (0.06)	1.19 (0.08)			0.69 (0.16)	0.59 (0.16)	0.64 (0.17)		
Concentration	Saffron (n = 68)	Mean (SE)	2.72 (0.13)	2.01 (0.13)	1.79 (0.11)	0.552	0.04	2.54 (0.19)	1.87 (0.18)	1.35 (0.19)	0.288	0.15
	Placebo (n = 64)	Mean (SE)	2.89 (0.16)	1.98 (0.12)	1.92 (0.12)			2.72 (0.19)	1.84 (0.23)	1.78 (0.23)		
Initiative	Saffron (n = 68)	Mean (SE)	2.93 (0.15)	2.03 (0.14)	1.82 (0.13)	0.929	0.04	3.51 (0.19)	2.46 (0.21)	1.78 (0.21)	0.032	0.37
	Placebo (n = 64)	Mean (SE)	2.84 (0.16)	2.03 (0.15)	1.80 (0.13)			3.30 (0.21)	2.30 (0.22)	2.30 (0.20)		
Interest	Saffron (n = 68)	Mean (SE)	2.25 (0.12)	1.54 (0.09)	1.46 (0.08)	0.301	0.23	2.19 (0.24)	1.82 (0.22)	1.57 (0.20)	0.015	0.45
	Placebo (n = 64)	Mean (SE)	2.03 (0.12)	1.53 (0.09)	1.48 (0.09)			1.95 (0.22)	1.80 (0.21)	1.78 (0.22)		
Pessimism	Saffron (n = 68)	Mean (SE)	2.96 (0.13)	2.38 (0.12)	2.15 (0.13)	0.680	0.14	2.90 (0.21)	2.03 (0.20)	1.81 (0.20)	0.859	0.03
	Placebo (n = 64)	Mean (SE)	3.03 (0.14)	2.38 (0.11)	2.06 (0.13)			3.23 (0.18)	2.27 (0.20)	2.20 (0.23)		
Suicidal ideation	Saffron (n = 68)	Mean (SE)	2.12 (0.12)	1.62 (0.10)	1.60 (0.11)	0.726	0.00	0.66 (0.13)	0.26 (0.08)	0.29 (0.10)	0.058	0.33
	Placebo (n = 64)	Mean (SE)	1.97 (0.12)	1.58 (0.12)	1.45 (0.11)			0.47 (0.12)	0.41 (0.11)	0.52 (0.14)		

[a]*p*-value repeated measures analysis of variance (ANOVA) time by group interaction; [b] Cohen's D effect size.

in total scores (Hermens et al., 2006; Kobak et al., 2008). Potential discrepancies in outcomes may be associated with the differing time intervals used in the measures, where the MADRS-S refers to the last three days while the MADRS queries the past week. It was noted by Svanborg and Asberg (1994) during the initial development of the MADRS-S that patients did not limit their ratings to the previous three days but instead rated the maximum severity of their symptoms. This has significant implications on the MADRS-S as an outcome measure for antidepressant trials. It is also possible that the non-concordant correlations in suicide ratings may be influenced by the knowledge of participants that serious suicidal ideation may result in study exclusion and withdrawal. In fact, in the current study, investigator-ratings of suicidal ideation were consistently lower than those indicated via self-reports at all time points. Potentially, participants may have been reluctant to disclose suicidal ideation to the investigator. However, this seems unlikely as disclosure via the MADRS-S would have also resulted in withdrawal from the study. Finally, many participants continued to remain depressed throughout the duration of the study, albeit at a reduced severity, which may have influenced their ratings throughout the study. Depression is associated with a negative cognitive bias, making it difficult to provide an objective assessment of the environment (Gotlib and Joormann, 2010). Moreover, literacy issues could also account for the moderated treatment outcomes from the MADRS-S. Interestingly, when participants were asked to provide satisfaction ratings using a simple and easy-to-understand single rating, participants in the saffron condition reported a greater likelihood of continuing to take saffron supplements after the completion of the study than participants in the placebo condition. It is important to note that lack of blinding is unlikely to account for the discordant findings as clinician ratings were conducted by a rater blinded to treatment conditions until the end of the trial. Furthermore, efficacy of participant blinding was high as only 25% of respondents correctly predicted treatment allocation.

The antidepressant efficacy of saffron in adults with depression has been confirmed via several meta-analyses. In randomised, placebo-controlled trials, large effect sizes have been identified for the treatment of mild-to-moderate adult depression. Saffron is also comparable in efficacy to the pharmaceutical antidepressants fluoxetine, citalopram and imipramine (Hausenblas et al., 2013; Lopresti and Drummond, 2014; Marx et al., 2019; Toth et al., 2018). As an adjunct to antidepressants, research is limited and inconsistent. The addition of crocin (an active constituent of saffron) to antidepressant medications (fluoxetine, sertraline, or citalopram) resulted in larger improvements in depressive symptoms compared with placebo (Talaei et al., 2015). In another study, the adjunct use of saffron with fluoxetine had no additional benefit compared with a placebo although there were significantly lower drop-out rates in the saffron group (Sahraian et al., 2016). Finally, in a study on patients with severe depression, the combination of fluoxetine and saffron for four weeks provided no additional antidepressant benefit compared with the addition of a placebo (Jelodar et al., 2018). However, these studies were hindered by the small sample sizes (40 in each study) and short study duration (four weeks) making it difficult to form definitive conclusions. In the current study, the large sample size (160 participants) allowed the detection of small-to-medium effect sizes. This study also lasted eight weeks, with differentiating effects occurring from weeks 4 to 8. A standardised saffron extract (affron®) was also used in this study, which ensures reproducibility in the quality of saffron used. This extract has also been investigated in several antidepressant trials with positive mood-enhancing effects (Kell et al., 2017; Lopresti and Drummond, 2017; Lopresti et al., 2018).

Several mechanisms of action may account for the putative antidepressant effect of saffron. Depression is associated with disturbances in several biological pathways, namely disturbances in monoaminergic activity such as serotonin, dopamine, and glutamate; dysregulation in hypothalamus-pituitary-adrenal (HPA) activity; chronic, low-grade inflammation; increased oxidative and nitrosative stress; and neuroprogression (Maes et al., 2011; Miller and Raison, 2015; Moylan et al., 2013). Evidence from *in-vitro* and *in-vivo* animal studies has demonstrated that saffron and its components impact on these mechanisms (Lopresti and Drummond, 2014). For example, the administration of a saffron extract dose-dependently increased brain concentrations of dopamine, and at high doses increased glutamate levels (Ettehadi et al., 2013). In another animal study, the administration of crocin modulated serotonergic activity in rats exposed to the non-selective serotonin receptor agonist, meta-chlorophenylpiperazine (Georgiadou et al., 2012). Saffron and its constituents, crocin, crocetin and safranal also modulate the activity of endogenous antioxidant enzymes, and have anti-inflammatory and immune-regulating effects (Boskabady and Farkhondeh, 2016; Boskabady et al., 2011; Poma et al., 2012; Razavi et al., 2013; Samarghandian et al., 2017). In addition, animal stress studies have confirmed that saffron modulates HPA activity by reducing plasma corticosterone concentrations (Halataei et al., 2011; Hooshmandi et al., 2011) and has neuroprotective effects through its influence on the neurotrophin, brain-derived neurotrophic factor (Ghasemi et al., 2014; Vahdati Hassani et al., 2014). Moreover, in a study on adults with mild-cognitive impairment, saffron intake was associated with changes in EEG activity, as demonstrated by improvements in the P300 response (Tsolaki et al., 2016). The latency of the P300 response is a physiological measure of psychomotor performance and decision making and is longer in depressed patients (Kalayam and Alexopoulos, 1999; Kindermann et al., 2000).

Limitations and directions for future research

Evidence for the antidepressant efficacy of saffron in adults is accumulating and the results from this study provide confirmation of its benefits as an adjunct to antidepressants. However, there are several limitations associated with this study. As has been discussed previously, the strongest support for the antidepressant efficacy of saffron was demonstrated via clinician- rather than self-administered assessment. Further research is required to help clarify possible reasons for these discrepant findings. Incorporating objective measures of change may be useful in the future including changes in cortisol, neurotrophins and inflammatory and oxidative stress markers. Changes in neurological activity through the measurement of EEG activity and cognitive testing may also be helpful as objective measures of change. These assessments have the advantage of clarifying the potential antidepressant mechanisms associated with saffron. Additional outcome measures that assess specific symptoms associated with depression such as sleep, appetite, motivation, cognitions and physical activity may also be helpful. This may be particularly useful as in the current study saffron seemed to be associated with improvements in sleep, drive and interest.

In this study recruitment occurred solely via social media promotion which may have skewed the population examined. This includes a greater tendency to recruit a cohort of younger age, high social media and technology users. Including a range of recruitment strategies may enhance the breadth of population characteristics. It must also be acknowledged that adherence to tablet intake was assessed only via participant self-report of remaining tablet numbers. The accuracy of these self-reports could not be confirmed and alternative or additional adherence measures in future studies should be considered. These include multi-measure approaches such as the use of diaries, questionnaires and pharmacokinetic measurements (Lam and Fresco, 2015).

In this study, the efficacy of saffron as an adjunct to antidepressant use in adults who continued to experience depressive symptoms was examined. This cohort of treatment-resistant participants is likely to have impacted on identified outcomes. In fact, almost 50% of participants reported taking antidepressants for two years or longer. Such treatment resistance may be associated with comorbid mental, physical, lifestyle and social factors that limit the efficacy of stand-alone natural and pharmacological treatments. The effects of saffron as adjunct in newly-prescribed antidepressant users will be important to examine in the future. This may be particularly important due to the adverse effects associated with pharmaceutical antidepressant use which are commonly reported reasons for their discontinuation. Given the preliminary positive effects of saffron on adverse effects, saffron could be used as an adjunctive agent given at the outset of antidepressant treatment to increase treatment efficacy and reduce potential adverse effects. Further confirmation of the effect of saffron in reducing adverse effects arising from pharmaceutical antidepressants is provided from two studies where saffron supplementation lowered sexual disturbances in men and women taking fluoxetine (Kashani et al., 2013; Modabbernia et al., 2012). The efficacy of adjunctive saffron use on specific antidepressant types and classes will also be important to investigate in future studies. In this study, approximately 55% of participants were taking an SSRI and 32% were taking an SNRI (the remaining were taking other classes of antidepressants). Whether saffron is more efficacious as an adjunct to a specific class of antidepressants requires further investigation.

The antidepressant effect of saffron was investigated over an eight-week period. The safety and efficacy of saffron over a longer duration requires further examination. The majority of previous studies on saffron have been four to eight weeks, although two studies of 12 weeks have been conducted (Mazidi et al., 2016; Moazen-Zadeh et al., 2017) with no identified adverse effects. However, as these studies investigated the effects of saffron as a stand-alone treatment, its safety and efficacy as an adjunctive agent over a longer period requires examination. Saffron was also administered at a dose of 14 mg twice daily from a saffron extract, standardised to contain $>$ 3.5% Lepticrosalides® (affron®). Future dose-escalation studies for treatment non-responders will be useful to examine the potential efficacy and safety of higher doses. Generalisation of the results of this study to other saffron extracts and the addition of saffron to cooking to promote antidepressant effects should be done with caution given the significant variance associated with the quality of saffron stigmas and the variability in extracts available on the market. The quality of herbal preparations can vary significantly due to seasonal variation, soil types, harvesting techniques, storage and extraction methods; this is particularly problematic for saffron, given its high price and risk of adulteration (Khilare et al., 2019).

Finally, the placebo effect in this and other antidepressant trials requires further consideration. In this study there was a 21% and 26% reduction in depressive symptoms based on the self-report and clinician-rated measures, respectively. Depression is a highly placebo-responsive condition with reported placebo response rates up to 40% in antidepressant clinical trials (Sonawalla and Rosenbaum, 2002). Reasons proposed for the placebo response include participant expectations, volunteer-investigator relationships, increases in motivation for change and improvements in symptoms resulting from the passage of time (Sonawalla and Rosenbaum, 2002). Placebos, despite being inert substances, are associated not only with cognitive adjustments but also with biological and neurochemical changes. For example, symptom reduction after administration of a placebo appears to involve the opioid system in patients with major depressive disorder (Pecina et al., 2015). Hence, it may be possible to enhance the efficacy of specific treatments by optimising nonspecific cognitive, behavioural and/or physiological placebo effects.

In conclusion, the results of this study provide conflicting evidence for the antidepressant benefits of a standardised saffron extract (affron®) as an adjunct to pharmaceutical medications in adults with persistent depression. The positive benefits were derived from the MADRS, a clinician-rated outcome measure, but not the self-rated MADRS. Saffron was well-tolerated with no significant adverse effects reported during this eight-week study. No between-group differences in quality of life as measured by the SF-36 were identified. Given the conflicting findings, further research is needed to clarify the clinical benefits of saffron as an adjunctive treatment for adults with persistent depressive symptoms despite antidepressant drug treatment. Further research will also be important to help understand the potential antidepressant actions of saffron, its efficacy and safety over a longer duration, its effects on different antidepressant classes, and if differing doses influence treatment outcomes.

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ORCID iDs

Adrian L Lopresti https://orcid.org/0000-0002-6409-7839
Sean D Hood https://orcid.org/0000-0003-2852-7923

References

Adli M, Baethge C, Heinz A, et al. (2005) Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed? A systematic review. *Eur Arch Psychiatry Clin Neurosci* 255: 387–400.

Akhondzadeh Basti A, Ghoreishi SA, Noorbala AA, et al. (2008) Petal and stigma of *Crocus sativus L.* in the treatment of depression: A pilot double-blind randomized trial. *J Med Plants* 7: 29–36.

Akhondzadeh S, Fallah-Pour H, Afkham K, et al. (2004) Comparison of *Crocus sativus L.* and imipramine in the treatment of mild to moderate depression: a pilot double-blind randomized trial [ISRCTN45683816]. *BMC Complement Altern Med* 4: 12.

Berm EJ, Hak E, Postma M, et al. (2015) Effects and cost-effectiveness of pharmacogenetic screening for CYP2D6 among older adults starting therapy with nortriptyline or venlafaxine: Study protocol for a pragmatic randomized controlled trial (CYSCEtrial). *Trials* 16: 37.

Bet PM, Hugtenburg JG, Penninx BW, et al. (2013) Side effects of antidepressants during long-term use in a naturalistic setting. *Eur Neuropsychopharmacol* 23: 1443–1451.

Bondolfi G, Jermann F, Rouget BW, et al. (2010) Self- and clinician-rated Montgomery–Åsberg Depression Rating Scale: Evaluation in clinical practice. *J Affect Disord* 121: 268–272.

Boskabady MH and Farkhondeh T (2016) Antiinflammatory, antioxidant, and immunomodulatory effects of *Crocus sativus L.* and its main constituents. *Phytother Res* 30: 1072–1094.

Boskabady MH, Seyedhosseini Tamijani SM, Rafatpanah H, et al. (2011) The effect of *Crocus sativus* extract on human lymphocytes' cytokines and T helper 2/T helper 1 balance. *J Med Food* 14: 1538–1545.

Burra TA, Chen E, McIntyre RS, et al. (2007) Predictors of self-reported antidepressant adherence. *Behav Med* 32: 127–134.

Cipriani A, Furukawa TA, Salanti G, et al. (2018) Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *Lancet* 391: 1357–1366.

Cuijpers P, Li J, Hofmann SG, et al. (2010) Self-reported versus clinician-rated symptoms of depression as outcome measures in psychotherapy research on depression: A meta-analysis. *Clin Psychol Rev* 30: 768–778.

Cunningham JL, Wernroth L, von Knorring L, et al. (2011) Agreement between physicians' and patients' ratings on the Montgomery–Åsberg depression rating scale. *J Affect Disord* 135: 148–153.

Dunlop BW, Li T, Kornstein SG, et al. (2010) Correlation between patient and clinician assessments of depression severity in the PREVENT study. *Psychiatry Res* 177: 177–183.

Ettehadi H, Mojabi SN, Ranjbaran M, et al. (2013) Aqueous extract of saffron (*Crocus sativus*) increases brain dopamine and glutamate concentrations in rats. *J Behav Brain Sci* 3: 315–319.

Fantino B and Moore N (2009) The self-reported Montgomery–Åsberg depression rating scale is a useful evaluative tool in major depressive disorder. *BMC Psychiatry* 9: 26.

Georgiadou G, Tarantilis PA and Pitsikas N (2012) Effects of the active constituents of *Crocus sativus L.*, crocins, in an animal model of obsessive-compulsive disorder. *Neurosci Lett* 528: 27–30.

Ghajar A, Neishabouri SM, Velayati N, et al. (2017) *Crocus sativus L.* versus citalopram in the treatment of major depressive disorder with anxious distress: A double-blind, controlled clinical trial. *Pharmacopsychiatry* 50: 152–160.

Ghasemi T, Abnous K, Vahdati F, et al. (2014) Antidepressant effect of *crocus sativus* aqueous extract and its effect on CREB, BDNF, and VGF transcript and protein levels in rat hippocampus. *Drug Res (Stuttg)* 65: 337–343.

Gotlib IH and Joormann J (2010) Cognition and depression: current status and future directions. *Annu Rev Clin Psychol* 6: 285–312.

Greenberg RP, Bornstein RF, Greenberg MD, et al. (1992) A meta-analysis of antidepressant outcome under 'blinder' conditions. *J Consult Clin Psychol* 60: 664–669; discussion 670–667.

Halataei BA, Khosravi M, Arbabian S, et al. (2011) Saffron (*Crocus sativus*) aqueous extract and its constituent crocin reduces stress-induced anorexia in mice. *Phytother Res* 25: 1833–1838.

Hausenblas HA, Saha D, Dubyak PJ, et al. (2013) Saffron (*Crocus sativus L.*) and major depressive disorder: A meta-analysis of randomized clinical trials. *J Integrat Med* 11: 377–383.

Hays RD, Sherbourne CD and Mazel RM (1993) The RAND 36-item health survey 1.0. *Health Econ* 2: 217–227.

Hermens ML, Ader HJ, van Hout HP, et al. (2006) Administering the MADRS by telephone or face-to-face: A validity study. *Ann Gen Psychiatry* 5: 3.

Hooshmandi Z, Rohani AH, Eidi A, et al. (2011) Reduction of metabolic and behavioral signs of acute stress in male Wistar rats by saffron water extract and its constituent safranal. *Pharma Biol* 49: 947–954.

Iannuzzo RW, Jaeger J, Goldberg JF, et al. (2006) Development and reliability of the HAM-D/MADRS interview: An integrated depression symptom rating scale. *Psychiatry Res* 145: 21–37.

Jakubovski E, Varigonda AL, Freemantle N, et al. (2016) Systematic review and meta-analysis: Dose-response relationship of selective serotonin reuptake inhibitors in major depressive disorder. *Am J Psychiatry* 173: 174–183.

Jelodar G, Javid Z, Sahraian A, et al. (2018) Saffron improved depression and reduced homocysteine level in patients with major depression: A randomized, double-blind study. *Avicenna J Phytomed* 8: 43–50.

Kalayam B and Alexopoulos GS (1999) Prefrontal dysfunction and treatment response in geriatric depression. *Arch Gen Psychiatry* 56: 713–718.

Kashani L, Raisi F, Saroukhani S, et al. (2013) Saffron for treatment of fluoxetine-induced sexual dysfunction in women: Randomized double-blind placebo-controlled study. *Hum Psychopharmacol* 28: 54–60.

Kell G, Rao A, Beccaria G, et al. (2017) Affron® a novel saffron extract (*Crocus sativus L*.) improves mood in healthy adults over 4 weeks in a double-blind, parallel, randomized, placebo-controlled clinical trial. *Complement Ther Med* 33: 58–64.

Khilare V, Tiknaik A, Prakash B, et al. (2019) Multiple tests on saffron find new adulterant materials and reveal that Ist grade saffron is rare in the market. *Food Chem* 272: 635–642.

Kindermann SS, Kalayam B, Brown GG, et al. (2000) Executive functions and P300 latency in elderly depressed patients and control subjects. *Am J Geriatr Psychiatry* 8: 57–65.

Kobak KA, Williams JB, Jeglic E, et al. (2008) Face-to-face versus remote administration of the Montgomery–Åsberg depression rating scale using videoconference and telephone. *Depress Anxiety* 25: 913–919.

Lam WY and Fresco P (2015) Medication adherence measures: An overview. *Biomed Res Int* 2015: 217047.

Lopresti AL and Drummond PD (2014) Saffron (*Crocus sativus*) for depression: A systematic review of clinical studies and examination of underlying antidepressant mechanisms of action. *Hum Psychopharmacol* 29: 517–527.

Lopresti AL and Drummond PD (2017) Efficacy of curcumin, and a saffron/curcumin combination for the treatment of major depression: A randomised, double-blind, placebo-controlled study. *J Affect Disord* 207: 188–196.

Lopresti AL, Drummond PD, Inarejos-Garcia AM, et al. (2018) Affron®, a standardised extract from saffron (*Crocus sativus L*.) for the treatment of youth anxiety and depressive symptoms: A randomised, double-blind, placebo-controlled study. *J Affect Disord* 232: 349–357.

Maes M, Leonard B, Fernandez A, et al. (2011) (Neuro)inflammation and neuroprogression as new pathways and drug targets in depression: From antioxidants to kinase inhibitors. *Prog Neuropsychopharmacol Biol Psychiatry* 35: 659–663.

Marx W, Lane M, Rocks T, et al. (2019) The effect of saffron supplementation on symptoms of depression and anxiety: A systematic review and meta-analysis. *Nutr Rev*. Epub ahead of print 28 May 2019. DOI: 10.1093/nutrit/nuz023.

Mazidi M, Shemshian M, Mousavi SH, et al. (2016) A double-blind, randomized and placebo-controlled trial of Saffron (*Crocus sativus L*.) in the treatment of anxiety and depression. *J Complement Integr Med* 13: 195–199.

McHorney CA, Ware JE, Jr and Raczek AE (1993) The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care* 31: 247–263.

Miller AH and Raison CL (2015) The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nat Rev Immunol* 16: 22–34.

Moazen-Zadeh E, Abbasi SH, Safi-Aghdam H, et al. (2017) Effects of saffron on cognition, anxiety, and depression in patients undergoing coronary artery bypass grafting: A randomized double-blind placebo-controlled trial. *J Altern Complement Med*. Epub ahead of print 29 November 2017. DOI: 10.1089/acm.2017.0173.

Modabbernia A, Sohrabi H, Nasehi AA, et al. (2012) Effect of saffron on fluoxetine-induced sexual impairment in men: randomized double-blind placebo-controlled trial. *Psychopharmacology* 223: 381–388.

Montgomery SA and Åsberg M (1979) A new depression scale designed to be sensitive to change. *Br J Psychiatry* 134: 382–389.

Moylan S, Maes M, Wray NR, et al. (2013) The neuroprogressive nature of major depressive disorder: pathways to disease evolution and resistance, and therapeutic implications. *Mol Psychiatry* 18: 595–606.

Papakostas GI, Thase ME, Fava M, et al. (2007) Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. *Biol Psychiatry* 62: 1217–1227.

Pecina M, Bohnert AS, Sikora M, et al. (2015) Association between placebo-activated neural systems and antidepressant responses: Neurochemistry of placebo effects in major depression. *JAMA Psychiatry* 72: 1087–1094.

Poma A, Fontecchio G, Carlucci G, et al. (2012) Anti-inflammatory properties of drugs from saffron crocus. *Antiinflamm Antiallergy Agents Med Chem* 11: 37–51.

Quilty LC, Robinson JJ, Rolland JP, et al. (2013) The structure of the Montgomery–Åsberg depression rating scale over the course of treatment for depression. *Int J Methods Psychiatr Res* 22: 175–184.

Razavi M, Hosseinzadeh H, Abnous K, et al. (2013) Crocin restores hypotensive effect of subchronic administration of diazinon in rats. *Iran J Basic Med Sci* 16: 64–72.

Reilly TJ, MacGillivray SA, Reid IC, et al. (2015) Psychometric properties of the 16-item quick inventory of depressive symptomatology: A systematic review and meta-analysis. *J Psychiatr Res* 60: 132–140.

Rush AJ, Trivedi MH, Wisniewski SR, et al. (2006) Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *Am J Psychiatry* 163: 1905–1917.

Sahraian A, Jelodar S, Javid Z, et al. (2016) Study the effects of saffron on depression and lipid profiles: A double blind comparative study. *Asian J Psychiatr* 22: 174–176.

Samarghandian S, Nezhad MA, Samini F, et al. (2017) The role of saffron in attenuating age-related oxidative damage in rat hippocampus. *Recent Pat Food Nutr Agric* 8: 183–189.

Sansone RA and Sansone LA (2012) Antidepressant adherence: Are patients taking their medications? *Innov Clin Neurosci* 9: 41–46.

Sonawalla SB and Rosenbaum JF (2002) Placebo response in depression. *Dialogues Clin Neurosci* 4: 105–113.

Soper DS (2019) *A-priori Sample Size Calculator for Student t-Tests [Software]*. Available at: http://www.danielsoper.com/statcalc.

Svanborg P and Asberg M (1994) A new self-rating scale for depression and anxiety states based on the Comprehensive Psychopathological Rating Scale. *Acta Psychiatr Scand* 89: 21–28.

Talaei A, Hassanpour Moghadam M, Sajadi Tabassi SA, et al. (2015) Crocin, the main active saffron constituent, as an adjunctive

treatment in major depressive disorder: A randomized, double-blind, placebo-controlled, pilot clinical trial. *J Affect Disord* 174: 51–56.

Toth B, Hegyi P, Lantos T, et al. (2018) The efficacy of saffron in the treatment of mild to moderate depression: A meta-analysis. *Planta Med*. Epub ahead of print 23 July 2018. DOI: 10.1055/a-0660-9565.

Tsolaki M, Karathanasi E, Lazarou I, et al. (2016) Efficacy and safety of *Crocus sativus L*. in patients with mild cognitive impairment: One year single-blind randomized, with parallel groups, clinical trial. *J Alzheimers Dis* 54: 129–133.

Uher R, Farmer A, Henigsberg N, et al. (2009) Adverse reactions to antidepressants. *Br J Psychiatry* 195: 202–210.

Uher R, Perlis RH, Placentino A, et al. (2012) Self-report and clinician-rated measures of depression severity: Can one replace the other? *Depress Anxiety* 29: 1043–1049.

Vahdati Hassani F, Naseri V, Razavi BM, et al. (2014) Antidepressant effects of crocin and its effects on transcript and protein levels of CREB, BDNF, and VGF in rat hippocampus. *Daru* 22: 16.

Ware JE, Jr and Sherbourne CD (1992) The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 30: 473–483.

Williams JB and Kobak KA (2008) Development and reliability of a structured interview guide for the Montgomery–Åsberg Depression Rating Scale (SIGMA). *Br J Psychiatry* 192: 52–58.